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(54) Title: CHOLESTEROL ABSORPTION INHIBITORS FOR THE TREATMENT OF DEMYELINATION

(57) Abstract: The present invention provides methods for treating demyelination and associated conditions by administering at least one sterol absorption inhibitor and compositions, therapeutic combinations and methods including : (a) at least one sterol absorption inhibitor; and (b) at least one demyelination treatment which can be useful for preventing or treating demyelination and associated conditions, such as multiple sclerosis.

CHOLESTEROL ABSORPTION INHIBITORS FOR THE TREATMENT OF DEMYELINATION

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CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority from U.S. Provisional Patent Application Serial No. 60/493,318, filed August 7, 2003 and U.S. Provisional Patent Application Serial No. 60/424,165, filed November 6, 2002.

10

BACKGROUND OF THE INVENTIONField of the Invention

The present invention relates to methods and therapeutic combinations for 15 treating and preventing demyelination in a subject comprising the administration of sterol absorption inhibitor(s).

Description

Nerve fibers are wrapped with many layers of insulation known as the myelin 20 sheath. Like insulation around an electrical wire, the myelin sheath permits electrical impulses to be conducted along the nerve fiber with speed and accuracy. When normal development of the myelin is impaired (for example in subjects having Tay-Sachs disease, Niemann-Pick disease, Gaucher's disease and Hurler's syndrome), permanent, extensive neurological defects can result. Also, the myelin sheath can be 25 damaged by stroke, inflammation, immune diseases, metabolic disorders, poison or drugs. If the sheath is able to regenerate itself, normal nerve function can be partially or fully restored. If demyelination is extensive, the underlying nerve can die and cause irreversible damage. Demyelination in the central nervous system (brain and spinal cord) occurs in several primary demyelinating diseases, such as multiple 30 sclerosis, acute disseminated encephalomyelitis, adrenoleukodystrophy, adrenomyeloneuropathy, Leber's hereditary optic atrophy and HTLV-associated myelopathy.

Multiple sclerosis ("MS") is characterized by the loss of patches of myelin in the 35 nerves of the eye, brain and/or spinal cord. It is believed that the body produces antibodies against its own myelin that provoke inflammation and damage the myelin

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sheath. Heredity and environment appear to play some role in the disease, although it is believed that a virus or unknown antigen somehow triggers the autoimmune process. Symptoms depend upon the area affected. Demyelination in nerve pathways that bring signals to muscles can produce problems with movement (motor symptoms), such as weakness, clumsiness, difficulty in walking or maintaining balance, tremor, double vision, problems with bladder or bowel control, stiffness, unsteadiness or unusual tiredness. Demyelination in nerve pathways that bring signals to the brain can cause sensory symptoms, such as numbness, tingling, dysesthesias, visual disturbances, sexual dysfunction, dizziness or vertigo. Magnetic resonance imaging (MRI) can reveal areas of the brain that have lost myelin, and may even distinguish areas of recent demyelination from areas that occurred some time ago.

Treatments for multiple sclerosis include injection with beta-interferon, which can decrease the frequency and occurrence of flare-ups and slow the progression to disability; injection with glatiramer acetate, which can reduce the frequency of relapses; or administration of corticosteroids, such as prednisone, to relieve acute symptoms. Recently, statins such as simvastatin and atorvastatin (HMG CoA reductase inhibitors) have been studied for their immunomodulatory effects in treating MS. C. Pelfrey, "ACTRIMS – ECTRIMS 2002 (Part II)", *IDDB Meeting Report*, September 18-21, 2002 Baltimore, Maryland, USA, (October 3, 2002).

There is a need in the art for improved compositions and treatments for demyelination and associated diseases such as multiple sclerosis.

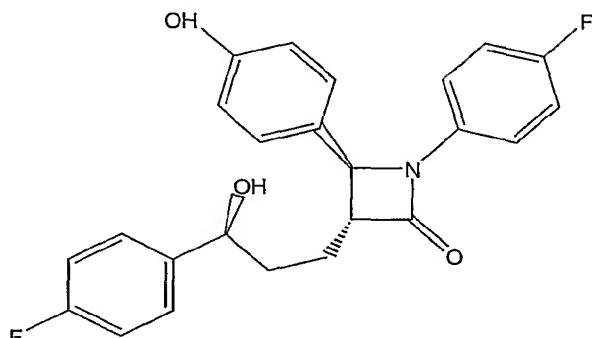
SUMMARY OF THE INVENTION

In one embodiment, there is provided a method of treating or preventing demyelination in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, there is provided a method of treating or preventing multiple sclerosis in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof.

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A method of treating or preventing demyelination in a subject is provided, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor represented by Formula (II) below:



5 (II)

or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, the present invention provides a composition comprising: (a) at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof and (b) at least one ant demyelination agent.

Therapeutic combinations also are provided comprising: (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof; and (b) a second amount of at least one ant demyelination agent, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of demyelination in a subject.

Pharmaceutical compositions for the treatment or prevention of demyelination in a subject, comprising a therapeutically effective amount of the above compounds, compositions or therapeutic combinations and a pharmaceutically acceptable carrier also are provided.

20 Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about."

DETAILED DESCRIPTION

According to F. Giubilei et al., "Blood Cholesterol and MRI Activity in First Clinical Episode Suggestive of Multiple Sclerosis", *Acta Neurol Scand* 2002; 106: 109-112, 111, a significant correlation was found between MS disease activity and both 5 total and LDL (low density lipoprotein) cholesterol levels. Lesions formed by demyelination are characterized by the presence of foamy macrophages containing cholesterol esters. J. Newcombe et al., "Low Density Lipoprotein Uptake by Macrophages in Multiple Sclerosis Plaques: Implication for Pathogenesis", *Neuropathol. Appl. Neurobiol.* 1994; 20:152-62, 152. There is evidence of early 10 involvement of LDL in the development of MS lesions. F. Giubilei at 111. A large proportion of the plasma LDL enters the parenchyma of MS plaques as a result of blood-brain barrier damage and is oxidatively modified in the lesion. Id. Lipid peroxidation and oxidized LDL uptake by infiltrating macrophages or microglial cells in 15 early stages of MS plaque development may play an important role in demyelination.

Id.

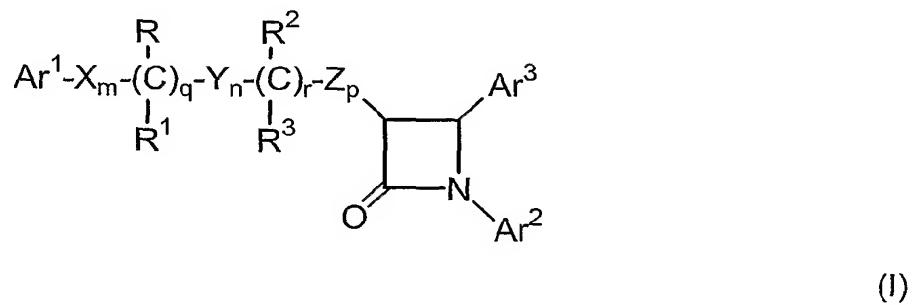
U.S. Patents Nos. 5,767,115, 5,624,920, 5,668,990, 5,656,624 and 5,688,787, respectively, disclose hydroxy-substituted azetidinone compounds and substituted β -lactam compounds useful for inhibiting the absorption of cholesterol, thereby lowering cholesterol levels and/or inhibiting the formation of cholesterol-containing lesions in 20 mammalian arterial walls. U.S. Patents Nos. 5,846,966 and 5,661,145, respectively, disclose hydroxy-substituted azetidinone compounds or substituted β -lactam compounds in combination with HMG CoA reductase inhibitors for preventing or treating atherosclerosis and reducing plasma cholesterol levels. Such compounds can also be useful in lowering C-reactive protein levels in subjects.

According to the present invention, these and other sterol absorption inhibitors discussed in detail below can be useful in preventing or treating demyelination and its associated conditions, such as primary demyelinating diseases including but not limited to multiple sclerosis, acute disseminated encephalomyelitis, adrenoleukodystrophy, adrenomyeloneuropathy, Leber's hereditary optic atrophy and 25 HTLV-associated myelopathy, and other conditions characterized by demyelination such as Tay-Sachs disease, Niemann-Pick disease, Gaucher's disease and Hurler's syndrome; or stroke, inflammation, immune diseases, metabolic disorders, poison or

drugs.

In one embodiment, the present invention is directed to compositions, pharmaceutical compositions, therapeutic combinations, kits and methods of treatment using the same comprising at least one (one or more) sterol absorption inhibitor(s). Suitable sterol absorption inhibitors include substituted azetidinone sterol absorption inhibitors, substituted β -lactam sterol absorption inhibitors or combinations thereof as discussed in detail below. As used herein, "sterol absorption inhibitor" means a compound capable of inhibiting the absorption of one or more sterols, including but not limited to cholesterol, phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol), when administered in a therapeutically effective (sterol absorption inhibiting) amount to a subject, such as a mammal or human. Other useful compositions, pharmaceutical compositions, therapeutic combinations, kits and methods of treatment using the same comprise at least one (one or more) 5α -stanol absorption inhibitor(s). As used herein, " 5α -stanol absorption inhibitor" means a compound capable of inhibiting the absorption of one or more 5α -stanols (such as cholestanol, 5α -campestanol, 5α -sitostanol), when administered in a therapeutically effective (5α -stanol absorption inhibiting) amount to a subject, such as a mammal or human.

In a preferred embodiment, sterol or 5α -stanol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (I) below:



25 or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula
(I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4 -substituted aryl;

Ar³ is aryl or R⁵-substituted aryl:

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X, Y and Z are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R² are independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁹ and -O(CO)NR⁶R⁷;

5 R¹ and R³ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

10 R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀₋₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶, -CH=CH-COOR⁶, -CF₃, -CN, -NO₂ and halogen;

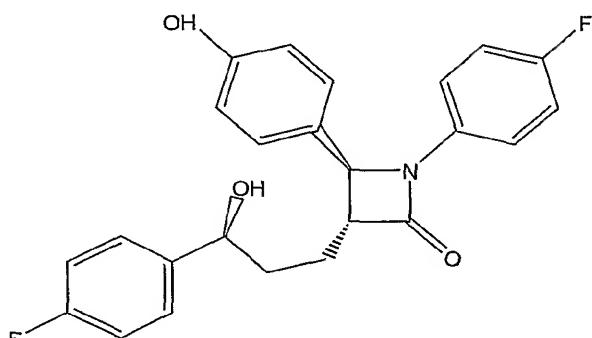
15 R⁵ is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀₋₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

20 R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

25 R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl.

Preferably, R⁴ is 1-3 independently selected substituents, and R⁵ is preferably 1-3 independently selected substituents.

In a preferred embodiment, a sterol or 5α -stanol absorption inhibitor of Formula (I) useful in the compositions, therapeutic combinations and methods of the present invention is represented by Formula (II) (ezetimibe) below:



5

(11)

or a pharmaceutically acceptable salt or solvate thereof. The compound of Formula (II) can be in anhydrous or hydrated form.

As used herein, the term "alkyl" or "lower alkyl" means straight or branched alkyl chains having from 1 to 6 carbon atoms and "alkoxy" means alkoxy groups having 1 to 6 carbon atoms. Non-limiting examples of lower alkyl groups include, for example methyl, ethyl, propyl, and butyl groups. Where an alkyl chain joins two other variables and is therefore bivalent, the term alkylene is used.

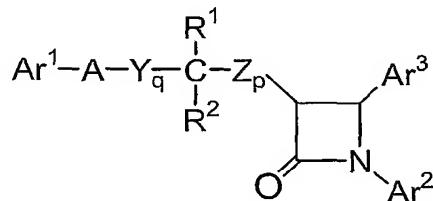
"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms, such as phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

The statements wherein, for example, R, R¹, R² and R³ are said to be independently selected from a group of substituents mean that R, R¹, R² and R³ are each independently selected, but also that where an R, R¹, R² and R³ variable occurs more than once in a molecule, each occurrence is independently selected (e.g., if R is -OR⁶, wherein R⁶ is hydrogen, R² can be -OR⁶ wherein R⁶ is lower alkyl). Those skilled in the art will recognize that the size and nature of the substituent(s) will affect the number of substituents that can be present.

Compounds of Formula I can be prepared by a variety of methods well known to those skilled in the art, for example such as are disclosed in U.S. Patents Nos. 5,631,365, 5,767,115, 5,846,966, 6,207,822, PCT Patent Application No. 02/079174

and PCT Patent Application WO 93/02048, each of which is incorporated herein by reference, and in the Example below.

Alternative sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (III) below:



(III)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (III) above:

Ar¹ is R³-substituted aryl;

Ar² is R⁴-substituted aryl;

Ar³ is R⁵-substituted aryl;

Y and Z are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(dilower alkyl)-;

A is selected from -O-, -S-, -S(O)- or -S(O)₂-;

R¹ is selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁹ and -O(CO)NR⁶R⁷; R² is selected from the group consisting of hydrogen, lower alkyl and aryl; or R¹ and R² together are =O;

q is 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

R⁵ is 1-3 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁-₅OR⁹, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂-lower alkyl, -NR⁶SO₂-aryl, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀-₂-alkyl, S(O)₀-₂-aryl, -O(CH₂)₁-₁₀-COOR⁶, -O(CH₂)₁-₁₀CONR⁶R⁷, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-COOR⁶, and -CH=CH-COOR⁶;

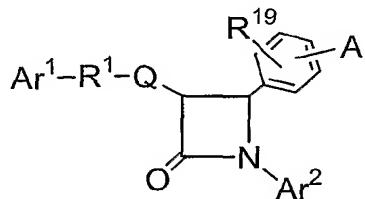
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R^3 and R^4 are independently 1-3 substituents independently selected from the group consisting of R^5 , hydrogen, p-lower alkyl, aryl, $-NO_2$, $-CF_3$ and p-halogeno;

R^6 , R^7 and R^8 are independently selected from the group consisting of 5 hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

Methods for making compounds of Formula III are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,688,990, which is incorporated herein by reference.

10 In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (IV):



(IV)

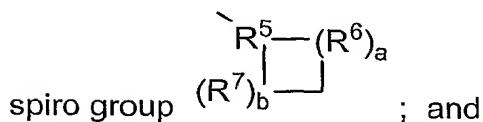
15 or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (IV) above:

A is selected from the group consisting of R^2 -substituted heterocycloalkyl, R^2 -substituted heteroaryl, R^2 -substituted benzofused heterocycloalkyl, and R^2 -substituted benzofused heteroaryl;

20 Ar^1 is aryl or R^3 -substituted aryl;

Ar^2 is aryl or R^4 -substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the



R^1 is selected from the group consisting of:

25 $-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

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$-(CH_2)_e-G-(CH_2)_r$, wherein G is $-O-$, $-C(O)-$, phenylene, $-NR^8-$ or $-S(O)_{0-2-}$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;
 $-(C_2-C_6$ alkenylene)-; and
 $-(CH_2)_f-V-(CH_2)_g$, wherein V is C_3-C_6 cycloalkylene, f is 1-5 and g is 0-5,
5 provided that the sum of f and g is 1-6;

R^5 is selected from:

$-CH-$, $-C(C_1-C_6$ alkyl)-, $-CF-$, $-C(OH)-$, $-C(C_6H_4-R^9)-$, $-N-$, or $-NO^-$;

R^6 and R^7 are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)-, $-C(di-(C_1-C_6)$ alkyl), $-CH=CH-$ and
10 $-C(C_1-C_6$ alkyl)=CH-; or R^5 together with an adjacent R^6 , or R^5 together with an adjacent R^7 , form a $-CH=CH-$ or a $-CH=C(C_1-C_6$ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^6 is $-CH=CH-$ or $-C(C_1-C_6$ alkyl)=CH-, a is 1; provided that when R^7 is $-CH=CH-$ or $-C(C_1-C_6$ alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R^6 's can be the same or different; and provided that when b is 2 or 3, the R^7 's can be the same or different;

and when Q is a bond, R^1 also can be selected from:

$-M-Y_d-C(R^{10})_h-Z_h-$, $-X_m-(C(R^{12})_s-Y_n-(C(R^{10})_t-Z_p-$ or $-X_j-(C(R^{10})_v-Y_k-S(O)_{0-2}-$;

where M is $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;

20 X, Y and Z are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)- and $-C(di-(C_1-C_6)$ alkyl);

R^{10} and R^{12} are independently selected from the group consisting of $-OR^{14}$, $-O(CO)R^{14}$, $-O(CO)OR^{16}$ and $-O(CO)NR^{14}R^{15}$;

25 R^{11} and R^{13} are independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl and aryl; or R^{10} and R^{11} together are $=O$, or R^{12} and R^{13} together are $=O$;
d is 1, 2 or 3;

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h is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

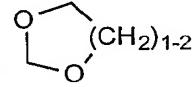
j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

R² is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl,

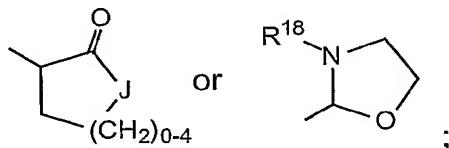
10 (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, R¹⁷-substituted aryl, R¹⁷-substituted benzyl, R¹⁷-substituted benzyloxy, R¹⁷-substituted aryloxy, halogeno, -NR¹⁴R¹⁵, NR¹⁴R¹⁵(C₁-C₆ alkylene)-, NR¹⁴R¹⁵C(O)(C₁-C₆ alkylene)-, -NHC(O)R¹⁶, OH, C₁-C₆ alkoxy, -OC(O)R¹⁶,

-COR¹⁴, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, NO₂, -S(O)₀₋₂R¹⁶,

15 SO₂NR¹⁴R¹⁵ and -(C₁-C₆ alkylene)COOR¹⁴; when R² is a substituent on a



heterocycloalkyl ring, R² is as defined, or is =O or ; and, where R² is a substituent on a substitutable ring nitrogen, it is hydrogen, (C₁-C₆)alkyl, aryl, (C₁-C₆)alkoxy, aryloxy, (C₁-C₆)alkylcarbonyl, arylcarbonyl, hydroxy, -(CH₂)₁₋₆CONR¹⁸R¹⁸,



20 wherein J is -O-, -NH-, -NR¹⁸- or -CH₂-;

R³ and R⁴ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₁-C₆)alkyl,

-OR¹⁴, -O(CO)R¹⁴, -O(CO)OR¹⁶, -O(CH₂)₁₋₅OR¹⁴, -O(CO)NR¹⁴R¹⁵, -NR¹⁴R¹⁵,

-NR¹⁴(CO)R¹⁵, -NR¹⁴(CO)OR¹⁶, -NR¹⁴(CO)NR¹⁵R¹⁹, -NR¹⁴SO₂R¹⁶, -COOR¹⁴,

25 -CONR¹⁴R¹⁵, -COR¹⁴, -SO₂NR¹⁴R¹⁵, S(O)₀₋₂R¹⁶, -O(CH₂)₁₋₁₀-COOR¹⁴,

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-O(CH₂)₁₋₁₀CONR¹⁴R¹⁵, -(C₁-C₆ alkylene)-COOR¹⁴, -CH=CH-COOR¹⁴, -CF₃, -CN, -NO₂ and halogen;

R⁸ is hydrogen, (C₁-C₆)alkyl, aryl (C₁-C₆)alkyl, -C(O)R¹⁴ or -COOR¹⁴;

R⁹ and R¹⁷ are independently 1-3 groups independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -COOH, NO₂, -NR¹⁴R¹⁵, OH and halogeno;

R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, aryl and aryl-substituted (C₁-C₆)alkyl;

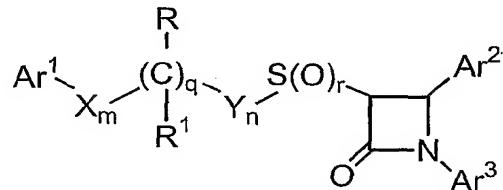
R¹⁶ is (C₁-C₆)alkyl, aryl or R¹⁷-substituted aryl;

R¹⁸ is hydrogen or (C₁-C₆)alkyl; and

R¹⁹ is hydrogen, hydroxy or (C₁-C₆)alkoxy.

Methods for making compounds of Formula IV are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,656,624, which is incorporated herein by reference.

In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (V):



(V)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (V) above:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X and Y are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(dilower alkyl)-;

R is $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^9$ or $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$; R^1 is hydrogen, lower alkyl or aryl; or R and R^1 together are $=\text{O}$;

q is 0 or 1;

r is 0, 1 or 2;

5 m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^9$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^9$, $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, -(lower alkylene) COOR^6 and $-\text{CH}=\text{CH-COOR}^6$;

10 R^5 is 1-5 substituents independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^9$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^9$, $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$, halogen, -(lower alkylene) COOR^6 and $-\text{CH}=\text{CH-COOR}^6$;

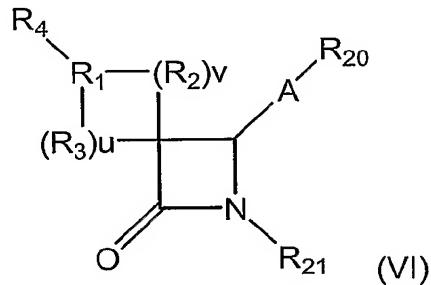
15 R^6 , R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

20 R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

25 R^{10} is 1-5 substituents independently selected from the group consisting of lower alkyl, $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^9$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^9$, $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $-\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen.

Methods for making compounds of Formula V are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,624,920, which is incorporated herein by reference.

5 In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VI):



or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein:

R₁ is

10 -CH-, -C(lower alkyl)-, -CF-, -C(OH)-, -C(C₆H₅)-, -C(C₆H₄-R₁₅)-,
 -N- or -⁺N O⁻;

R₂ and R₃ are independently selected from the group consisting of:

-CH₂-, -CH(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and -C(lower alkyl)=CH-; or
 R₁ together with an adjacent R₂, or R₁ together with an adjacent R₃, form a
 15 -CH=CH- or a -CH=C(lower alkyl)- group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R₂ is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R₃ is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R₂'s can be the same or different; and provided that when u is 2 or 3, the R₃'s can be the same or
 20 different;

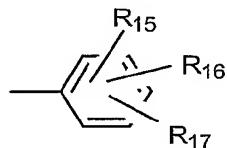
R₄ is selected from B-(CH₂)_mC(O)-, wherein m is 0, 1, 2, 3, 4 or 5;
 B-(CH₂)_q-, wherein q is 0, 1, 2, 3, 4, 5 or 6; B-(CH₂)_e-Z-(CH₂)_r-, wherein Z is -O-,
 -C(O)-, phenylene, -N(R₈)- or -S(O)O-2-, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5,
 provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6; B-(C₂-C₆ alkenylene)-; B-(C₄-C₆ alkadienylene)-; B-(CH₂)_t-Z-(C₂-C₆ alkenylene)-, wherein Z is as defined above,
 25

and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6; B-(CH₂)_f-V-(CH₂)_g-, wherein V is C₃-C₆ cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6; B-(CH₂)_t-V-(C₂-C₆ alkenylene)- or B-(C₂-C₆ alkenylene)-5 V-(CH₂)_t-, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

10 B-(CH₂)_a-Z-(CH₂)_b-V-(CH₂)_d-, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6; or T-(CH₂)_s-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R₁ and R₄ together form the group $\overset{\text{I}}{\text{B}}\text{-CH}=\text{C-}$;

15 B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, 20 alkoxy carbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, -CF₃, -OCF₃, benzyl, R₇-benzyl, benzyloxy, R₇-benzyloxy, phenoxy, R₇-phenoxy, dioxolanyl, NO₂, -N(R₈)(R₉), N(R₈)(R₉)-lower alkylene-, N(R₈)(R₉)-lower alkylenyloxy-, OH, halogeno, -CN, -N₃, -NHC(O)OR₁₀, -NHC(O)R₁₀, R₁₁O₂SNH-, (R₁₁O₂S)₂N-, -S(O)₂NH₂, -S(O)O-2R₈, tert-25 butyldimethyl-silyloxymethyl, -C(O)R₁₂, -COOR₁₉, -CON(R₈)(R₉), -CH=CHC(O)R₁₂, -lower alkylene-C(O)R₁₂, R₁₀C(O)(lower alkyleneoxy)-, N(R₈)(R₉)C(O)(lower

alkyleneoxy)- and $-\text{CH}_2-\text{N}(\text{R}_{13})-$ for substitution on ring carbon atoms,

and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OR10, -C(O)R10, OH, N(R8)(R9)-lower alkylene-, N(R8)(R9)-lower alkyleneoxy-, -S(O)2NH₂ and 2-(trimethylsilyl)-ethoxymethyl;

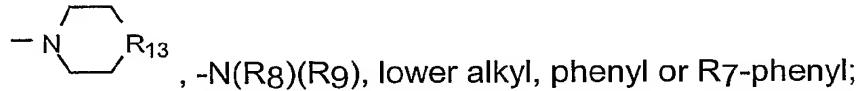
5 R₇ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO₂, -N(R8)(R9), OH, and halogeno;

R₈ and R₉ are independently selected from H or lower alkyl;

10 R₁₀ is selected from lower alkyl, phenyl, R₇-phenyl, benzyl or R₇-benzyl;

R₁₁ is selected from OH, lower alkyl, phenyl, benzyl, R₇-phenyl or R₇-benzyl;

R₁₂ is selected from H, OH, alkoxy, phenoxy, benzyloxy,



R₁₃ is selected from -O-, -CH₂-, -NH-, -N(lower alkyl)- or -NC(O)R₁₉;

15 R₁₅, R₁₆ and R₁₇ are independently selected from the group consisting of H and the groups defined for W; or R₁₅ is hydrogen and R₁₆ and R₁₇, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

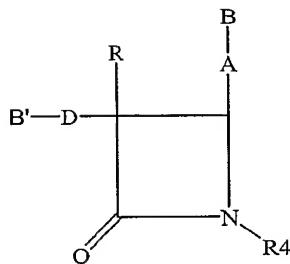
R₁₉ is H, lower alkyl, phenyl or phenyl lower alkyl; and

20 R₂₀ and R₂₁ are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

25 Methods for making compounds of Formula VI are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,698,548, which is incorporated herein by reference.

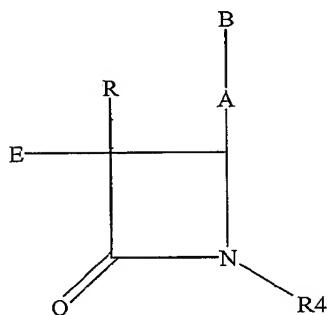
In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formulas (VIIA) and (VIIB):

- 17 -



(VIIA)

and



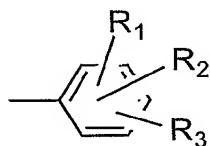
(VIIIB)

5

or a pharmaceutically acceptable salt or solvate thereof,
wherein:

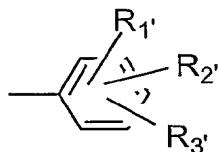
A is $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$ or $-(\text{CH}_2)_p-$ wherein p is 0, 1 or 2;

B is



10

B' is



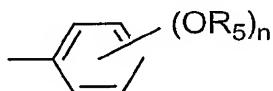
D is $-(\text{CH}_2)_m\text{C}(\text{O})-$ or $-(\text{CH}_2)_q-$ wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

15 E is C₁₀ to C₂₀ alkyl or $-\text{C}(\text{O})-(\text{C}_9 \text{ to } \text{C}_{19})\text{-alkyl}$, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

R is hydrogen, C₁-C₁₅ alkyl, straight or branched, saturated or containing one or more double bonds, or B-(CH₂)_r-, wherein r is 0, 1, 2, or 3;

R₁, R₂, R₃, R_{1'}, R_{2'}, and R_{3'} are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO₂, NH₂, OH, halogeno, lower alkylamino, dilower alkylamino, -NHC(O)OR₅, R₆O₂SNH- and -S(O)₂NH₂;

R₄ is



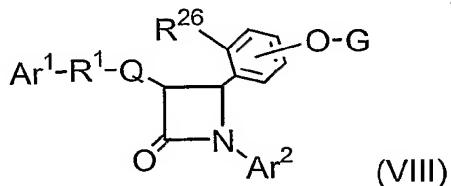
5

wherein n is 0, 1, 2 or 3;

R₅ is lower alkyl; and

R₆ is OH, lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO₂, NH₂, OH, halogeno, lower alkylamino and dilower alkylamino; or a pharmaceutically acceptable salt thereof or a solvate thereof.

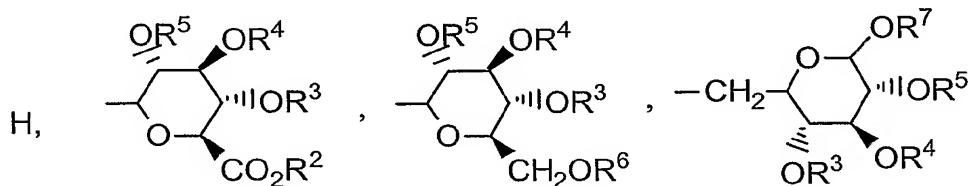
In another embodiment, sterol absorption inhibitors useful in the compositions and methods of the present invention are represented by Formula (VIII):

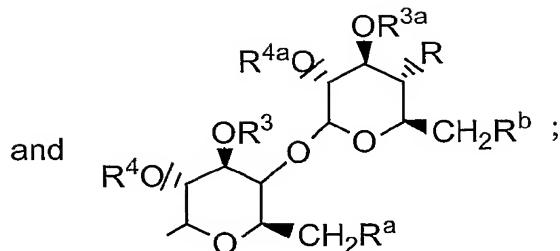


15 or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (VIII) above,

R²⁶ is H or OG¹;

G and G¹ are independently selected from the group consisting of





provided that when R²⁶ is H or

OH, G is not H;

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, -NH₂, azido, (C₁-C₆)alkoxy(C₁-C₆)-alkoxy or -W-R³⁰;

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R³¹)-, -NH-C(O)-N(R³¹)- and -O-C(S)-N(R³¹)-;

R² and R⁶ are independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl and aryl(C₁-C₆)alkyl;

R³, R⁴, R⁵, R⁷, R^{3a} and R^{4a} are independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, -C(O)(C₁-C₆)alkyl and -C(O)aryl;

R³⁰ is selected from the group consisting of R³²-substituted T, R³²-substituted-T-(C₁-C₆)alkyl, R³²-substituted-(C₂-C₄)alkenyl, R³²-substituted-(C₁-C₆)alkyl, R³²-substituted-(C₃-C₇)cycloalkyl and R³²-substituted-(C₃-C₇)cycloalkyl(C₁-C₆)alkyl;

R³¹ is selected from the group consisting of H and (C₁-C₄)alkyl;

T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R³² is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C₁-C₄)alkyl, -OH, phenoxy, -CF₃, -NO₂, (C₁-C₄)alkoxy, methylenedioxy, oxo, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, -N(CH₃)₂, -C(O)-NH(C₁-C₄)alkyl, -C(O)-N((C₁-C₄)alkyl)₂, -C(O)-(C₁-C₄)alkyl, -C(O)-(C₁-C₄)alkoxy and pyrrolidinylcarbonyl; or R³² is a covalent bond and R³¹, the nitrogen to which it is

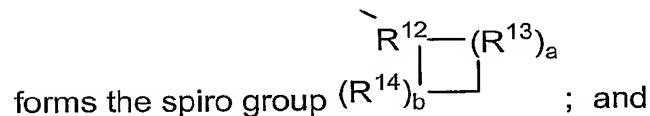
- 20 -

attached and R³² form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C₁-C₄)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar¹ is aryl or R¹⁰-substituted aryl;

5 Ar² is aryl or R¹¹-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone,



R¹ is selected from the group consisting of

-(CH₂)_q-, wherein q is 2-6, provided that when Q forms a spiro ring, q

10 can also be zero or 1;

-(CH₂)_e-E-(CH₂)_r-, wherein E is -O-, -C(O)-, phenylene, -NR²²- or

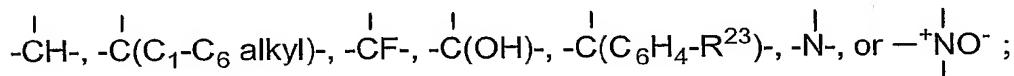
-S(O)O-2-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

-(C₂-C₆)alkenylene-; and

-(CH₂)_f-V-(CH₂)_g-, wherein V is C₃-C₆ cycloalkylene, f is 1-5 and g is

15 0-5, provided that the sum of f and g is 1-6;

R¹² is



R¹³ and R¹⁴ are independently selected from the group consisting of

-CH₂-, -CH(C₁-C₆ alkyl)-, -C(di-(C₁-C₆) alkyl), -CH=CH- and

20 -C(C₁-C₆ alkyl)=CH-; or R¹² together with an adjacent R¹³, or R¹² together with an adjacent R¹⁴, form a -CH=CH- or a -CH=C(C₁-C₆ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero;

provided that when R¹³ is -CH=CH- or -C(C₁-C₆ alkyl)=CH-, a is 1;

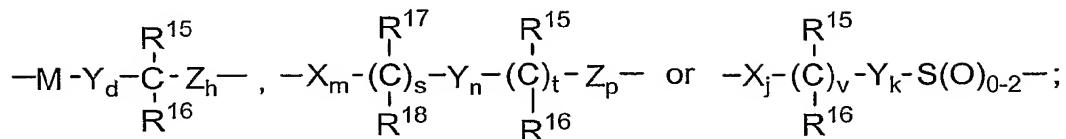
provided that when R¹⁴ is -CH=CH- or -C(C₁-C₆ alkyl)=CH-, b is 1;

25 provided that when a is 2 or 3, the R¹³'s can be the same or different; and

provided that when b is 2 or 3, the R¹⁴'s can be the same or different;

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and when Q is a bond, R¹ also can be:



M is -O-, -S-, -S(O)- or -S(O)2-;

X, Y and Z are independently selected from the group consisting of

5 -CH₂-, -CH(C₁-C₆)alkyl- and -C(di-C₁-C₆)alkyl);

R¹⁰ and R¹¹ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₁-C₆)alkyl, -OR¹⁹, -O(CO)R¹⁹, -O(CO)OR²¹, -O(CH₂)₁₋₅OR¹⁹, -O(CO)NR¹⁹R²⁰, -NR¹⁹R²⁰, -NR¹⁹(CO)R²⁰, -NR¹⁹(CO)OR²¹, -NR¹⁹(CO)NR²⁰R²⁵, -NR¹⁹SO₂R²¹, -COOR¹⁹, -CONR¹⁹R²⁰, -COR¹⁹, -SO₂NR¹⁹R²⁰, S(O)₀₋₂R²¹, -O(CH₂)₁₋₁₀-COOR¹⁹, -O(CH₂)₁₋₁₀CONR¹⁹R²⁰, -(C₁-C₆ alkylene)-COOR¹⁹, -CH=CH-COOR¹⁹, -CF₃, -CN, -NO₂ and halogen;

15 R¹⁵ and R¹⁷ are independently selected from the group consisting of -OR¹⁹, -O(CO)R¹⁹, -O(CO)OR²¹ and -O(CO)NR¹⁹R²⁰;

R¹⁶ and R¹⁸ are independently selected from the group consisting of H, (C₁-C₆)alkyl and aryl; or R¹⁵ and R¹⁶ together are =O, or R¹⁷ and R¹⁸ together are =O;

20 d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4;

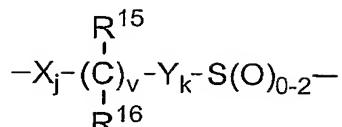
provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

25 v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

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and when Q is a bond and R¹ is $-\overset{\substack{R^{15} \\ | \\ X_j-(C)_v-Y_k-S(O)_{0-2}-}}{R^{16}}$, Ar¹ can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R¹⁹ and R²⁰ are independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl and aryl-substituted (C₁-C₆)alkyl;

R²¹ is (C₁-C₆)alkyl, aryl or R²⁴-substituted aryl;

R²² is H, (C₁-C₆)alkyl, aryl (C₁-C₆)alkyl, -C(O)R¹⁹ or -COOR¹⁹;

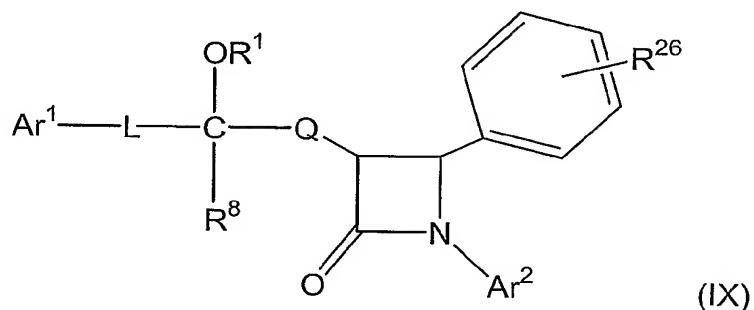
R²³ and R²⁴ are independently 1-3 groups independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -COOH, NO₂,

-NR¹⁹R²⁰, -OH and halogeno; and

R²⁵ is H, -OH or (C₁-C₆)alkoxy.

Methods for making compounds of Formula VIII are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,756,470, which is incorporated herein by reference.

In another embodiment, sterol absorption inhibitors useful in the compositions and methods of the present invention are represented by Formula (IX) below:

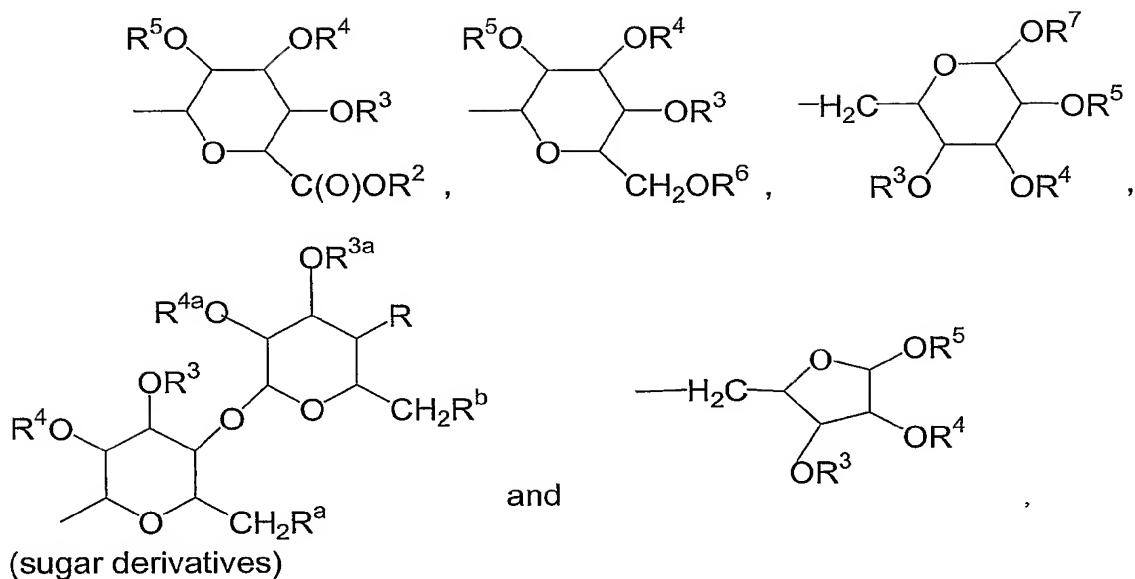


or a pharmaceutically acceptable salt or solvate thereof, wherein in Formula (IX):

R¹ is selected from the group consisting of H, G, G¹, G², -SO₃H and -PO₃H;

G is selected from the group consisting of: H,

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wherein R, R^a and R^b are each independently selected from the group consisting of H, -OH, halo, -NH₂, azido, (C₁-C₆)alkoxy(C₁-C₆)alkoxy or -W-R³⁰;

W is independently selected from the group consisting of

5 -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R³¹)-, -NH-C(O)-N(R³¹)- and
-O-C(S)-N(R³¹)-;

R² and R⁶ are each independently selected from the group consisting of H, (C₁-C₆)alkyl, acetyl, aryl and aryl(C₁-C₆)alkyl;

10 R³, R⁴, R⁵, R⁷, R^{3a} and R^{4a} are each independently selected from the group consisting of H, (C₁-C₆)alkyl, acetyl, aryl(C₁-C₆)alkyl, -C(O)(C₁-C₆)alkyl and -C(O)aryl;

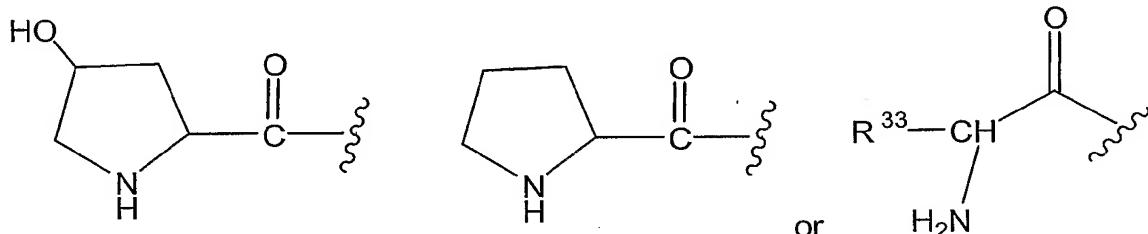
15 R³⁰ is independently selected from the group consisting of R³²-substituted T, R³²-substituted-T-(C₁-C₆)alkyl, R³²-substituted-(C₂-C₄)alkenyl, R³²-substituted-(C₁-C₆)alkyl, R³²-substituted-(C₃-C₇)cycloalkyl and R³²-substituted-(C₃-C₇)cycloalkyl(C₁-C₆)alkyl;

R³¹ is independently selected from the group consisting of H and (C₁-C₄)alkyl;

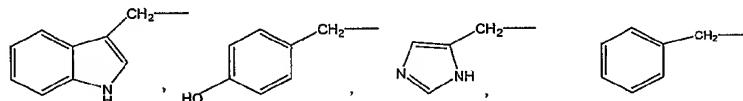
T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R³² is independently selected from 1-3 substituents which are each independently selected from the group consisting of H, halo, (C₁-C₄)alkyl, -OH, phenoxy, -CF₃, -NO₂, (C₁-C₄)alkoxy, methylenedioxy, oxo, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, -N(CH₃)₂, -C(O)-NH(C₁-C₄)alkyl, -C(O)-N((C₁-C₄)alkyl)₂, -C(O)-(C₁-C₄)alkyl, -C(O)-(C₁-C₄)alkoxy and pyrrolidinylcarbonyl; or R³² is a covalent bond and R³¹, the nitrogen to which it is attached and R³² form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C₁-C₄)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

10 G¹ is represented by the structure:



wherein R³³ is independently selected from the group consisting of unsubstituted alkyl, R³⁴-substituted alkyl, (R³⁵)(R³⁶)alkyl-,

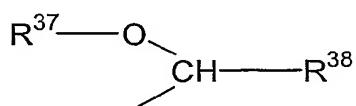


15 R³⁴ is one to three substituents, each R³⁴ being independently selected from the group consisting of HOOC-, HO-, HS-, (CH₃)S-, H₂N-, (NH₂)(NH)C(NH)-, (NH₂)C(O)- and HOOCCH(NH₃⁺)CH₂SS-;

R³⁵ is independently selected from the group consisting of H and NH₂-;

20 R³⁶ is independently selected from the group consisting of H, unsubstituted alkyl, R³⁴-substituted alkyl, unsubstituted cycloalkyl and R³⁴-substituted cycloalkyl;

G² is represented by the structure:



- 25 -

wherein R^{37} and R^{38} are each independently selected from the group consisting of (C_1-C_6)alkyl and aryl;

R^{26} is one to five substituents, each R^{26} being independently selected from the group consisting of:

- 5 a) H;
- b) -OH;
- c) -OCH₃;
- d) fluorine;
- e) chlorine;
- 10 f) -O-G;
- g) -O-G¹;
- h) -O-G²;
- i) -SO₃H; and
- j) -PO₃H;

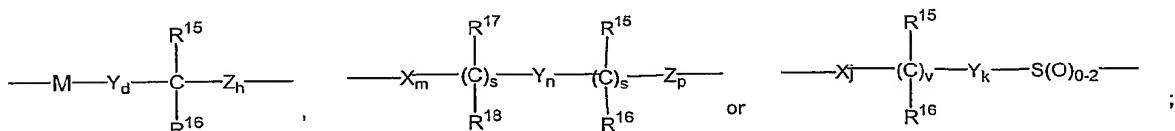
15 provided that when R^1 is H, R^{26} is not H, -OH, -OCH₃ or -O-G;

Ar^1 is aryl, R^{10} -substituted aryl, heteroaryl or R^{10} -substituted heteroaryl;

Ar^2 is aryl, R^{11} -substituted aryl, heteroaryl or R^{11} -substituted heteroaryl;

L is selected from the group consisting of:

- a) a covalent bond;
- 20 b) -(CH₂)_q-, wherein q is 1-6;
- c) -(CH₂)_e-E-(CH₂)_r-, wherein E is -O-, -C(O)-, phenylene, -NR²²- or -S(O)₀₋₂-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;
- d) -(C₂-C₆)alkenylene-;
- e) -(CH₂)_f-V-(CH₂)_g-, wherein V is C₃-C₆cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; and
- 25 f)



wherein M is -O-, -S-, -S(O)- or -S(O)₂-;

X, Y and Z are each independently selected from the group consisting of

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-CH₂-, -CH(C₁-C₆)alkyl- and -C(di-(C₁-C₆)alkyl)-;

R⁸ is selected from the group consisting of H and alkyl;

R¹⁰ and R¹¹ are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of (C₁-C₆)alkyl, -OR¹⁹, -O(CO)R¹⁹, -O(CO)OR²¹, -O(CH₂)₁₋₅OR¹⁹, -O(CO)NR¹⁹R²⁰, -

5 NR¹⁹R²⁰, -NR¹⁹(CO)R²⁰, -NR¹⁹(CO)OR²¹,

-NR¹⁹(CO)NR²⁰R²⁵, -NR¹⁹SO₂R²¹, -COOR¹⁹, -CONR¹⁹R²⁰, -COR¹⁹, -

SO₂NR¹⁹R²⁰, S(O)O-2R²¹, -O(CH₂)₁₋₁₀-COOR¹⁹, -O(CH₂)₁₋₁₀CONR¹⁹R²⁰, -(C₁-C₆ alkylene)-COOR¹⁹, -CH=CH-COOR¹⁹, -CF₃, -CN, -NO₂ and halo;

10 R¹⁵ and R¹⁷ are each independently selected from the group consisting of -OR¹⁹, -OC(O)R¹⁹, -OC(O)OR²¹, -OC(O)NR¹⁹R²⁰;

R¹⁶ and R¹⁸ are each independently selected from the group consisting of H, (C₁-C₆)alkyl and aryl;

or R¹⁵ and R¹⁶ together are =O, or R¹⁷ and R¹⁸ together are =O;

15 d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

s is 0 or 1;

t is 0 or 1;

m, n and p are each independently selected from 0-4;

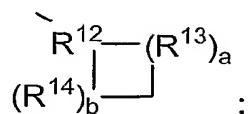
20 provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

provided that when p is 0 and t is 1, the sum of m, n and p is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

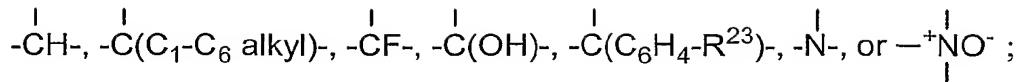
v is 0 or 1;

j and k are each independently 1-5, provided that the sum of j, k and v is 1-5;

25 Q is a bond, -(CH₂)_q-, wherein q is 1-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group



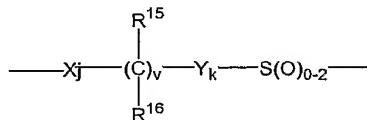
wherein R¹² is



R¹³ and R¹⁴ are each independently selected from the group consisting of -CH₂-, -CH(C₁-C₆ alkyl)-, -C(di-(C₁-C₆) alkyl), -CH=CH- and -C(C₁-C₆ alkyl)=CH-; or R¹² together with an adjacent R¹³, or R¹² together with an adjacent R¹⁴, form a -CH=CH- or a -CH=C(C₁-C₆ alkyl)- group;

5 a and b are each independently 0, 1, 2 or 3, provided both are not zero; provided that when R¹³ is -CH=CH- or -C(C₁-C₆ alkyl)=CH-, a is 1; provided that when R¹⁴ is -CH=CH- or -C(C₁-C₆ alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R¹³'s can be the same or different; and provided that when b is 2 or 3, the R¹⁴'s 10 can be the same or different;

and when Q is a bond and L is



15

then Ar¹ can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R¹⁹ and R²⁰ are each independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl and aryl-substituted (C₁-C₆)alkyl;

20 R²¹ is (C₁-C₆)alkyl, aryl or R²⁴-substituted aryl;

R²² is H, (C₁-C₆)alkyl, aryl (C₁-C₆)alkyl, -C(O)R¹⁹ or -COOR¹⁹;

R²³ and R²⁴ are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -COOH, NO₂, -NR¹⁹R²⁰, -OH and halo; and

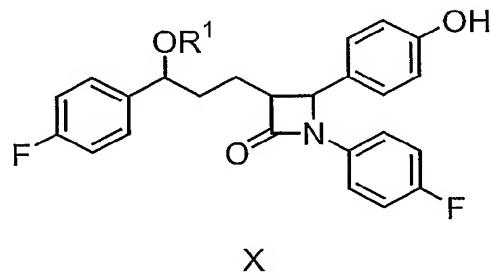
25 R²⁵ is H, -OH or (C₁-C₆)alkoxy.

Examples of compounds of Formula (IX) which are useful in the methods and combinations of the present invention and methods for making such compounds are

disclosed in U.S. Patent Application Serial No. 10/166,942, filed June 11, 2002, incorporated herein by reference.

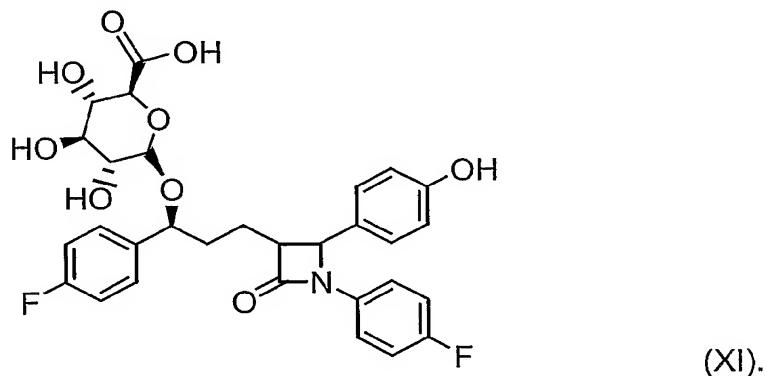
An example of a useful compound of this invention is one represented by the formula X:

5



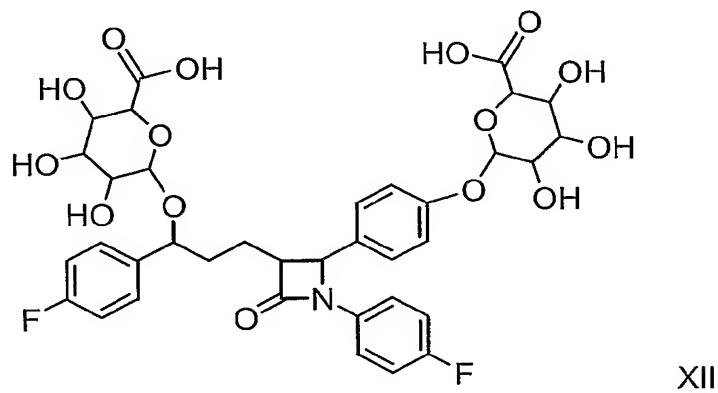
wherein R¹ is defined as above.

A more preferred compound is one represented by formula XI:



10

Another useful compound is represented by Formula XII:



Other useful substituted azetidinone compounds include N-sulfonyl-2-azetidinones such as are disclosed in U.S. Patent No. 4,983,597, ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates such as are disclosed in Ram et al., Indian J.

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Chem. Sect. B. 29B, 12 (1990), p. 1134-7, and diphenyl azetidinones and derivatives disclosed in U.S. Patent Publication Nos. 2002/0039774, 2002/0128252, 2002/0128253 and 2002/0137689, and WO 2002/066464, each of which is incorporated by reference herein.

5 The compounds of Formulae I-XII can be prepared by known methods, including the methods discussed above and, for example, WO 93/02048 describes the preparation of compounds wherein -R¹-Q- is alkylene, alkenylene or alkylene interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 describes the preparation of compounds wherein Q is a spirocyclic group; WO 95/08532
10 describes the preparation of compounds wherein -R¹-Q- is a hydroxy-substituted alkylene group; PCT/US95/03196 describes compounds wherein -R¹-Q- is a hydroxy-substituted alkylene attached to the Ar¹ moiety through an -O- or S(O)0-2- group; and U.S. Serial No. 08/463,619, filed June 5, 1995, describes the preparation
15 of compounds wherein -R¹-Q- is a hydroxy-substituted alkylene group attached the azetidinone ring by a -S(O)0-2- group.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including enantiomers, stereoisomers, rotamers, tautomers and racemates of the compounds of Formulae I-XII are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of the Formulae I-XII. Isomers may also include geometric isomers, e.g., when a double bond is present.

20 Those skilled in the art will appreciate that for some of the compounds of the Formulas I-XII, one isomer will show greater pharmacological activity than other isomers.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, 30 malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the

free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in 5 polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, 10 potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

As used herein, "solvate" means a molecular or ionic complex of molecules or 15 ions of solvent with those of solute (for example, one or more compounds of Formulae I-XII, isomers of the compounds of Formulae I-XII, or prodrugs of the compounds of Formulae I-XII). Non-limiting examples of useful solvents include polar, protic solvents such as water and/or alcohols (for example methanol).

Prodrugs of the compounds of Formulae I-XII are contemplated as being part of this invention. As used herein, "prodrug" means compounds that are drug precursors 20 which, following administration to a patient, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

The daily dose of the sterol absorption inhibitor(s) administered to the subject 25 can range from about 0.1 to about 1000 mg per day, preferably about 0.25 to about 50 mg/day, and more preferably about 10 mg per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

For administration of pharmaceutically acceptable salts of the above 30 compounds, the weights indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

5 The term "therapeutically effective amount" means that amount of a therapeutic agent of the composition, such as a sterol absorption inhibitor(s), antidyelination agent and other pharmacological or therapeutic agents described below, that will elicit a biological or medical response of a tissue, system, or subject that is being sought by the administrator (such as a researcher, doctor or veterinarian) which includes alleviation of the symptoms of the condition or disease being treated and the prevention, slowing or halting of progression of the condition (demyelination and its symptom(s)).

10 Examples of suitable subjects that can be treated according to the methods of the present invention include mammals, such as humans or dogs, and other animals.

15 As used herein, "combination therapy" or "therapeutic combination" means the administration of two or more therapeutic agents, such as sterol absorption inhibitor(s) and antidyelination agent(s), to prevent or treat demyelination or any of its associated conditions, such as are discussed above. As used herein, "demyelination" means insufficient or loss of myelin on the nerves. Such administration includes coadministration of these therapeutic agents in a substantially simultaneous manner, such as in a single tablet or capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each therapeutic agent. Also, such administration includes use of each type of therapeutic agent in a sequential manner. In either case, 20 the treatment using the combination therapy will provide beneficial effects in treating the demyelination condition. A potential advantage of the combination therapy disclosed herein may be a reduction in the required amount of an individual therapeutic compound or the overall total amount of therapeutic compounds that are effective in treating the demyelination condition. By using a combination of 25 therapeutic agents, the side effects of the individual compounds can be reduced as compared to a monotherapy, which can improve patient compliance. Also, therapeutic agents can be selected to provide a broader range of complimentary effects or complimentary modes of action.

30 In another embodiment, the present invention provides a therapeutic combination comprising (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt thereof or a solvate thereof; and (b) a second amount of at least one antidyelination agent or treatment, wherein the first amount

and the second amount together comprise a therapeutically effective amount for the treatment or prevention of demyelination or lessening or amelioration of one or more symptoms of a condition associated with demyelination.

In another embodiment, the present invention provides a pharmaceutical composition for the treatment or prevention of diabetes and/or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically effective amount of a composition comprising (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt thereof or a solvate thereof; (b) a second amount of at least one ant demyelination agent and (c) a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides a method of treating or preventing demyelination in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of a composition comprising (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt thereof or a solvate thereof; and (b) a second amount of at least one ant demyelination agent to prevent or treat demyelination or any of its symptoms in the subject.

Useful ant demyelination agents include beta-interferon (such as AVONEX® which is available from Biogen, Inc. and BETASERON® which is available from Berlex Laboratories), which can decrease the frequency and occurrence of flare-ups and slow the progression to disability, glatiramer acetate (such as COPAXONE® which is available from Teva Neuroscience, Inc.), which can reduce the frequency of relapses, and/or administration of corticosteroids, such as prednisone (available from Roxane), to relieve acute symptoms. The amount of respective ant demyelination agent to be administered to the subject readily can be determined by one skilled in the art from the Physician's Desk Reference (56th Ed. 2002) at pages 1013-1016, 988-995, 3306-3310 and 3064-3066, incorporated herein by reference.

Also useful with the present invention are compositions or therapeutic combinations that can further comprise one or more pharmacological or therapeutic agents or drugs such as cholesterol biosynthesis inhibitors and/or lipid-lowering agents discussed below.

Non-limiting examples of cholesterol biosynthesis inhibitors for use in the compositions, therapeutic combinations and methods of the present invention include competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis, squalene synthase inhibitors, squalene epoxidase inhibitors and mixtures thereof. Non-limiting examples of suitable HMG CoA reductase inhibitors include statins such as atorvastatin (for example LIPITOR® which is available from Pfizer), lovastatin (for example MEVACOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), fluvastatin, simvastatin (for example ZOCOR® which is available from Merck & Co.), cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate) and pitavastatin (such as NK-104 of Negma Kowa of Japan). Preferred HMG CoA reductase inhibitors include atorvastatin and simvastatin. Generally, a total daily dosage of cholesterol biosynthesis inhibitor(s) can range from about 0.1 to about 160 mg per day, and preferably about 0.2 to about 80 mg/day in single or 2-3 divided doses.

Also useful with the present invention are compositions or therapeutic combinations that can further comprise at least one (one or more) activators for peroxisome proliferator-activated receptors (PPAR), such as peroxisome proliferator-activated receptor alpha (PPAR α), peroxisome proliferator-activated receptor gamma (PPAR γ) and peroxisome proliferator-activated receptor delta (PPAR δ). PPAR α activator compounds are useful for, among other things, lowering triglycerides, moderately lowering LDL levels and increasing HDL levels. Useful examples of PPAR α activators include fibrates, such as clofibrate, gemfibrozil and fenofibrate. The PPAR activator(s) are administered in a therapeutically effective amount to treat the specified condition, for example in a daily dose preferably ranging from about 50 to about 3000 mg per day.

The compositions, therapeutic combinations or methods of the present invention can further comprise one or more bile acid sequestrants such as cholestyramine, colestipol and colesevelam hydrochloride. Generally, a total daily dosage of bile acid sequestrant(s) can range from about 1 to about 50 grams per day, and preferably about 2 to about 16 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise one or more ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above. The IBAT inhibitors can inhibit bile acid transport to reduce LDL cholesterol levels. Non-limiting examples of suitable IBAT inhibitors include benzothiepines such as are disclosed in PCT Patent Application WO 00/38727 which is incorporated herein by reference. Generally, a total daily dosage of IBAT inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.1 to about 50 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise nicotinic acid (niacin) and/or derivatives thereof, such as NIASPAN® (niacin extended-release tablets) which are available from Kos. Generally, a total daily dosage of nicotinic acid or a derivative thereof can range from about 500 to about 10,000 mg/day, preferably about 1000 to about 8000 mg/day, and more preferably about 3000 to about 6000 mg/day in single or divided doses.

The compositions or treatments of the present invention can further comprise one or more AcylCoA:Cholesterol O-acyltransferase ("ACAT") Inhibitors, which can reduce LDL and VLDL levels. Non-limiting examples of useful ACAT inhibitors include avasimibe. Generally, a total daily dosage of ACAT inhibitor(s) can range from about 0.1 to about 1000 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise one or more Cholesteryl Ester Transfer Protein ("CETP") Inhibitors. CETP is responsible for the exchange or transfer of cholesteryl ester carrying HDL and triglycerides in VLDL. Non-limiting examples of suitable CETP inhibitors are disclosed in PCT Patent Application No. WO 00/38721 and U.S. Patent No. 6,147,090, which are incorporated herein by reference. Generally, a total daily dosage of CETP inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.5 to about 20 mg/kg body weight/day in single or divided doses.

The compositions or treatments of the present invention can further comprise probucol or derivatives thereof, which can reduce LDL levels. Generally, a total daily dosage of probucol or derivatives thereof can range from about 10 to about 2000

mg/day, and preferably about 500 to about 1500 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise low-density lipoprotein (LDL) receptor activators such as HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity. Generally, a total daily dosage of LDL receptor activator(s) can range from about 1 to about 1000 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise fish oil, which contains Omega 3 fatty acids (3-PUFA), which can reduce VLDL and triglyceride levels. Generally, a total daily dosage of fish oil or Omega 3 fatty acids can range from about 1 to about 30 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise natural water soluble fibers, such as psyllium, guar, oat and pectin, which can reduce cholesterol levels. Generally, a total daily dosage of natural water soluble fibers can range from about 0.1 to about 10 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise plant sterols, plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine, which can reduce cholesterol levels. Generally, a total daily dosage of plant sterols, plant stanols and/or fatty acid esters of plant stanols can range from about 0.5 to about 20 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise antioxidants, such as probucol, tocopherol, ascorbic acid, β -carotene and selenium, or vitamins such as vitamin B₆ or vitamin B₁₂. Generally, a total daily dosage of antioxidants or vitamins can range from about 0.05 to about 10 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise monocyte and macrophage inhibitors such as polyunsaturated fatty acids, gene therapy and use of recombinant proteins such as recombinant apo E. Generally, a total daily dosage of these agents can range from about 0.01 to about 1000 mg/day in single or 2-4 divided doses.

The compositions, therapeutic combinations or methods of the present

invention can further comprise one or more cardiovascular agents or blood modifiers.

Mixtures of any of the pharmacological or therapeutic agents described above can be used in the compositions and therapeutic combinations of these other embodiments of the present invention.

5 The compositions and therapeutic combinations of the present invention can be administered to a subject in need of such treatment in a therapeutically effective amount to treat demyelination and its associated conditions as discussed above. The compositions and treatments can be administered by any suitable means which produce contact of these compounds with the site of action in the body, for example in
10 the plasma, liver or small intestine of a subject.

15 The daily dosage for the various compositions and therapeutic combinations described above can be administered to a subject in a single dose or in multiple subdoses, as desired. Subdoses can be administered 2 to 6 times per day, for example. Sustained release dosages can be used. Where the ant demyelination agent and sterol absorption inhibitor(s) are administered in separate dosages, the
15 number of doses of each component given per day may not necessarily be the same, e.g., one component may have a greater duration of activity and will therefore need to be administered less frequently.

20 The compositions, therapeutic combinations or medicaments of the present invention can further comprise one or more pharmaceutically acceptable carriers, one or more excipients and/or one or more additives. The pharmaceutical compositions can comprise about 1 to about 99 weight percent of active ingredient (such as one or more compounds of Formula I-XII), and preferably about 5 to about 95 percent active ingredient.

25 Useful pharmaceutically acceptable carriers can be either solid, liquid or gas. Non-limiting examples of pharmaceutically acceptable carriers include solids and/or liquids such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, ethanol, glycerol, water and the like. The amount of carrier in the treatment composition or therapeutic combination can range from about 5 to about 99 weight
30 percent of the total weight of the treatment composition or therapeutic combination. Non-limiting examples of suitable pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders such as starch, polyvinyl

pyrrolidone or cellulose ethers, disintegrants such as sodium starch glycolate, crosslinked polyvinyl pyrrolidone or croscarmellose sodium, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, wetting agents such as sodium lauryl sulfate, emulsifiers and the like. The amount of excipient or additive 5 can range from about 0.1 to about 95 weight percent of the total weight of the treatment composition or therapeutic combination. One skilled in the art would understand that the amount of carrier(s), excipients and additives (if present) can vary. Further examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions can be found in A. Gennaro (ed.), Remington: 10 The Science and Practice of Pharmacy, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Useful solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. An example of a preparation of a preferred solid form dosage formulation is provided below.

15 Useful liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

20 Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

25 Also useful are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

30 Preferably the compound is administered orally.

In another embodiment, the present invention provides the use of at least one compound represented by Formulae (I-XII) for manufacture of a medicament (such as

one of the compositions discussed above) for the treatment of demyelination and its associated conditions.

The following formulation exemplifies one of the dosage forms of this invention.

10 In the formulation, the term "Active Compound I" designates a sterol absorption inhibitor such as any of the compounds of Formulas I-XII described herein above and the term "Active Compound II" designates an ant demyelination agent described herein above.

EXAMPLE

<u>Tablets</u>		
<u>No.</u>	<u>Ingredient</u>	<u>mg/tablet</u>
1	Active Compound I	10
2	Lactose monohydrate NF	55
3	Microcrystalline cellulose NF	20
4	Povidone USP (K29-32)	4
5	Croscarmellose sodium NF	8
6	Sodium lauryl sulfate NF	2
7	Magnesium stearate NF	1
	Total	100

15 In the present invention, the above-described tablet can be coadministered with an injection, tablet, capsule, etc. comprising a dosage of Active Compound II as described above.

Method of Manufacture

Mix Item No. 4 with purified water in suitable mixer to form binder solution. Spray the binder solution and then water over Items 1, 2 and 6 and a portion of item 5 in a fluidized bed processor to granulate the ingredients. Continue fluidization to dry the damp granules. Screen the dried granule and blend with Item No. 3 and the remainder of Item No. 5. Add Item No. 7 and mix. Compress the mixture to appropriate size and weight on a suitable tablet machine.

For coadministration in separate tablets or capsules, representative formulations comprising a sterol absorption inhibitor such as are discussed above are well known in the art and representative formulations comprising an ant demyelination agent such as are discussed above are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for sterol absorption inhibitors may readily be modified using the knowledge of one skilled in the art.

Since the present invention relates to treating demyelination by treatment with a combination of active ingredients wherein the active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a pharmaceutical composition comprising at least one ant demyelination medication and a separate pharmaceutical composition comprising at least one sterol absorption inhibitor as described above. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g., oral and parenteral) or are administered at different dosage intervals.

The treatment compositions and therapeutic combinations of the present invention can inhibit the intestinal absorption of sterols in subjects and can be useful in the treatment and/or prevention of demyelination and associated conditions, such as multiple sclerosis, in subjects, in particular in mammals.

The compositions and therapeutic combinations of the present invention can reduce plasma concentration of at least one sterol selected from the group consisting of cholesterol, phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol), and/or 5 α -stanols (such as cholestanol, 5 α -campestanol, 5 α -sitostanol), and mixtures thereof. The plasma concentration can be reduced by administering to a subject in need of such treatment an effective amount of at least one treatment composition comprising at least one sterol or 5 α -stanol absorption inhibitor described above. The reduction in plasma concentration of sterols or 5 α -stanols can range from about 1 to about 70 percent, and preferably about 10 to about 50 percent. Methods of measuring serum total blood cholesterol and total LDL cholesterol are well known to

those skilled in the art and for example include those disclosed in PCT WO 99/38498 at page 11, incorporated by reference herein. Methods of determining levels of other sterols in serum are disclosed in H. Gylling et al., "Serum Sterols During Stanol Ester Feeding in a Mildly Hypercholesterolemic Population", *J. Lipid Res.* 40: 593-600 5 (1999), incorporated by reference herein.

These sterol absorption inhibitors can be useful in treating or preventing vascular inflammation. Vascular stimuli to mammals, such as cellular injury or inflammation, may lead to the production of various proteins, commonly called acute response proteins, in the body. One particular type of acute phase protein is C-reactive protein (CRP). Manufactured in the liver and deposited in damaged tissue, CRP is found in high levels in inflammatory fluids and in both the intimal layer of the atherosclerotic artery and within the lesions of atherosclerotic plaque. These sterol absorption inhibitors can be useful for lowering or controlling c-reactive protein blood levels in a subject to less than about 3.4 mg/dL. Preferably, the C-reactive protein 10 blood levels in a subject are reduced or controlled to less than 1.0 mg/dL by the methods of the present invention. More preferably, the C-reactive protein blood levels in a subject are reduced or controlled to less than 0.4 mg/dL by the methods of the 15 present invention. C-reactive protein assays and methodologies for the same are available from Behring Diagnostics Inc., of Somerville, NJ. Moreover, methods for 20 analyzing c-reactive proteins are described in U.S. Patents Nos. 5,358,852; 6,040,147; and 6,277,584, whose contents are incorporated herein by reference.

25 Illustrating the invention is the following example of preparation of a compound of Formula II which, however, is not to be considered as limiting the invention to their details. Unless otherwise indicated, all parts and percentages in the following examples, as well as throughout the specification, are by weight.

EXAMPLE

30 PREPARATION OF COMPOUND OF FORMULA (II)

Step 1): To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in CH₂Cl₂ (200 ml), was added 4-dimethylaminopyridine (2.5 g, 0.02 mol) and

triethylamine (84.7 ml, 0.61 mol) and the reaction mixture was cooled to 0°C. Methyl-4-(chloroformyl)butyrate (50 g, 0.3 mol) was added as a solution in CH₂Cl₂ (375 ml) dropwise over 1 h, and the reaction was allowed to warm to 22°C. After 17 h, water and H₂SO₄ (2N, 100 ml), was added the layers were separated, and the organic layer 5 was washed sequentially with NaOH (10%), NaCl (sat'd) and water. The organic layer was dried over MgSO₄ and concentrated to obtain a semicrystalline product.

Step 2): To a solution of TiCl₄ (18.2 ml, 0.165 mol) in CH₂Cl₂ (600 ml) at 0°C, was added titanium isopropoxide (16.5 ml, 0.055 mol). After 15 min, the product of Step 1 (49.0 g, 0.17 mol) was added as a solution in CH₂Cl₂ (100 ml). After 5 min., 10 diisopropylethylamine (DIPEA) (65.2 ml, 0.37 mol) was added and the reaction mixture was stirred at 0°C for 1 h, the reaction mixture was cooled to -20°C, and 4-benzyloxybenzylidine(4-fluoro)aniline (114.3 g, 0.37 mol) was added as a solid. The reaction mixture was stirred vigorously for 4 h at -20°C, then acetic acid was added as a solution in CH₂Cl₂ dropwise over 15 min, the reaction mixture was allowed to warm 15 to 0°C, and H₂SO₄ (2N) was added. The reaction mixture was stirred an additional 1 h, the layers were separated, washed with water, separated and the organic layer was dried. The crude product was crystallized from ethanol/water to obtain the pure intermediate.

Step 3): To a solution of the product of Step 2 (8.9 g, 14.9 mmol) in toluene 20 (100 ml) at 50°C, was added N,O-bis(trimethylsilyl)acetamide (BSA) (7.50 ml, 30.3 mmol). After 0.5 h, solid TBAF (0.39 g, 1.5 mmol) was added and the reaction mixture stirred at 50°C for an additional 3 h. The reaction mixture was cooled to 22°C, CH₃OH (10 ml), was added. The reaction mixture was washed with HCl (1N), NaHCO₃ (1N) and NaCl (sat'd.), and the organic layer was dried over MgSO₄.

Step 4): To a solution of the product of Step 3 (0.94 g, 2.2 mmol) in CH₃OH (3 ml), was added water (1 ml) and LiOH·H₂O (102 mg, 2.4 mmole). The reaction mixture was stirred at 22°C for 1 h and then additional LiOH·H₂O (54 mg, 1.3 mmole) was added. After a total of 2 h, HCl (1N) and EtOAc was added, the layers were separated, the organic layer was dried and concentrated in *vacuo*. To a solution of

the resultant product (0.91 g, 2.2 mmol) in CH_2Cl_2 at 22°C , was added ClCOCOCl (0.29 ml, 3.3 mmol) and the mixture stirred for 16 h. The solvent was removed in *vacuo*.

Step 5): To an efficiently stirred suspension of 4-fluorophenylzinc chloride (4.4 mmol) prepared from 4-fluorophenylmagnesium bromide (1M in THF, 4.4 ml, 4.4 mmol) and ZnCl_2 (0.6 g, 4.4 mmol) at 4°C , was added tetrakis(triphenylphosphine)palladium (0.25 g, 0.21 mmol) followed by the product of Step 4 (0.94 g, 2.2 mmol) as a solution in THF (2 ml). The reaction was stirred for 1 h at 0°C and then for 0.5 h at 22°C . HCl (1N, 5 ml) was added and the mixture was extracted with EtOAc. The organic layer was concentrated to an oil and purified by silica gel chromatography to obtain 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(3-oxo-3-phenylpropyl)-2-azetidinone:

HRMS calc'd for $\text{C}_{24}\text{H}_{19}\text{F}_2\text{NO}_3$ = 408.1429, found 408.1411.

Step 6): To the product of Step 5 (0.95 g, 1.91 mmol) in THF (3 ml), was added (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole (120 mg, 0.43 mmol) and the mixture was cooled to -20°C . After 5 min, borohydride-dimethylsulfide complex (2M in THF, 0.85 ml, 1.7 mmol) was added dropwise over 0.5 h. After a total of 1.5 h, CH_3OH was added followed by HCl (1 N) and the reaction mixture was extracted with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. ^1H in CDCl_3 d H3 = 4.68. J = 2.3 Hz. Cl (M^+H) 500.

Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1). ^1H in CDCl_3 d H3 = 4.69. J = 2.3 Hz. Cl (M^+H) 500.

To a solution of compound 6A-1 (0.4 g, 0.8 mmol) in ethanol (2 ml), was added 10% Pd/C (0.03 g) and the reaction mixture was stirred under a pressure (60 psi) of H_2 gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to obtain compound 6A. Mp 164-166 $^\circ\text{C}$; Cl (M^+H) 410. $[\alpha]_D^{25} = -28.1^\circ$ (c 3, CH_3OH). Elemental analysis calc'd for $\text{C}_{24}\text{H}_{21}\text{F}_2\text{NO}_3$: C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

Similarly treat compound 6B-1 to obtain compound 6B.

Mp 129.5-132.5°C; Cl (M⁺H) 410. Elemental analysis calc'd for C₂₄H₂₁F₂NO₃: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

Step 6' (Alternative): To a solution of the product of Step 5 (0.14 g, 0.3 mmol) in ethanol (2 ml), was added 10% Pd/C (0.03 g) and the reaction was stirred under a pressure (60 psi) of H₂ gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to afford a 1:1 mixture of compounds 6A and 6B.

Hypothetical In Vivo Evaluation

The compound of Formula II (or any cholesterol absorption inhibitor discussed above) is administered to rodents which have been induced to develop experimental autoimmune encephalomyelitis ("EAE"), a model of human multiple sclerosis and demyelinating disease. Useful rodents can include C57BL/6 mice (obtained from the Jackson Laboratory or Charles River Laboratories) immunized with myelin oligodendrocyte protein (MOG) 35-55 peptide, SJL/J (also available from Jackson Laboratory or Charles River Laboratories) mice immunized with proteolipid protein (PLP) peptides, or Lewis, BN or DA rats (obtained from Charles River Laboratories or Harlan Laboratories) immunized with guinea pig spinal cord homogenate or myelin basic protein (MBP). All immunizations are performed by emulsifying the inducing peptide in either incomplete Freund's adjuvant or complete Freund's adjuvant, with or without pertussis toxin administration (as described in *Current Protocols in Immunology*, Unit 15, John Wiley & Sons, Inc. NY, or Tran et al, *Eur. J. Immunol.* 30:1410, 2002 or H. Butzkeuven et al, *Nat. Med.* 8:613, 2002).

Alternatively, the compound of Formula II (or any cholesterol absorption inhibitor discussed above) is administered to anti-MBP T cell receptor transgenic mice (as in Grewal et al *Immunity* 14:291, 2001), which naturally develop EAE disease.

Alternatively the compound of Formula II (or any cholesterol absorption inhibitor discussed above) is administered to rodents adoptively transferred with MBP-specific, PLP-specific or MOG-specific T cell lines (as described in *Current Protocols in Immunology*, Unit 15, John Wiley & Sons, Inc. NY).

Alternatively, the compound of Formula II (or any cholesterol absorption inhibitor discussed above) is administered to SJL/J or C57BL/6 mice which can be

induced to develop a profound demyelinating disease by intracerebral inoculation with Theiler's murine encephalomyelitis virus (as described in Pope et al, *J. Immunol.* 156:4050, 1994) or by intraperitoneal injection of Simliki Forest virus (as described in Soiliu-Hanninen et al, *J. Virol.* 68:6291, 1994).

5 The compound is administered at a dosage of 0.1-50 mg/kg/day either in the diet or by systemic oral, subcutaneous or intraperitoneal administration over a period of 4-10 weeks. Animals are scored daily for clinical disease score as described in *Current Protocols in Immunology*, Unit 15, John Wiley & Sons, Inc. NY, or Tran et al, *Eur. J. Immunol.* 30:1410, 2002 or H. Butzkeuven et al, *Nat. Med.* 8:613, 2002). At a
10 specified period of compound administration, animals are euthanized by CO₂ asphyxiation and histological, immunohistochemical and immunological parameters measured as in Tran et al, *Eur. J. Immunol.* 30:1410, 2002 or H. Butzkeuven et al, *Nat. Med.* 8:613, 2002. Serum lipoprotein and cholesterol measurements will be made by standard techniques well known to those skilled in the art.

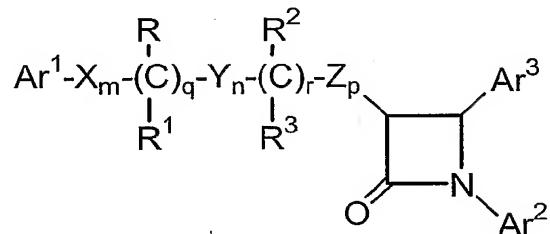
15 It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications that are within the
20 spirit and scope of the invention, as defined by the appended claims.

THEREFORE, WE CLAIM:

1. A method of treating or preventing demyelination in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof.

2. The method according to claim 1, wherein the at least one sterol absorption inhibitor is selected from the group consisting of compounds represented by:

(a) Formula (I):



(I)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein in Formula (I):

Ar¹ and Ar² are independently selected from the group consisting of aryl and R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X, Y and Z are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R² are independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁹ and -O(CO)NR⁶R⁷;

R¹ and R³ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

- 46 -

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

⁴ R is 1-5 substituents independently selected from the group consisting of

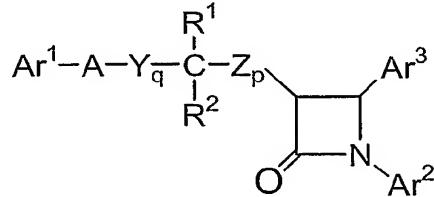
5 lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀₋₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶, -CH=CH-COOR⁶, -CF₃, -CN, -NO₂ and halogen;

10 ⁵ R is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀₋₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

15 ⁶ R, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

⁹ R is lower alkyl, aryl or aryl-substituted lower alkyl;

(b) Formula (III):



(III)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (III) above:

¹ Ar is R³-substituted aryl;

25 ² Ar is R⁴-substituted aryl;

³ Ar is R⁵-substituted aryl;

Y and Z are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$ and $-\text{C}(\text{dilower alkyl})-$;

A is selected from $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$;

5 R¹ is selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^9$ and $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$; R² is selected from the group consisting of hydrogen, lower alkyl and aryl; or R¹ and R² together are =O;

q is 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

10 R⁵ is 1-3 substituents independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^9$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^9$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^9$, $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{-lower alkyl}$, $-\text{NR}^6\text{SO}_2\text{-aryl}$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{-alkyl}$, $\text{S}(\text{O})_{0-2}\text{-aryl}$, $-\text{O}(\text{CH}_2)_{1-10}\text{-COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-COOR⁶, and

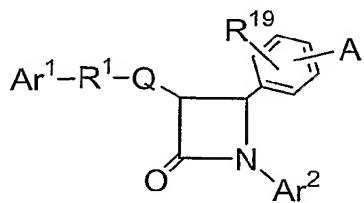
15 $-\text{CH}=\text{CH-COOR}^6$;

R³ and R⁴ are independently 1-3 substituents independently selected from the group consisting of R⁵, hydrogen, p-lower alkyl, aryl, $-\text{NO}_2$, $-\text{CF}_3$ and p-halogeno;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

20 R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl;

(c) Formula (IV):



(IV)

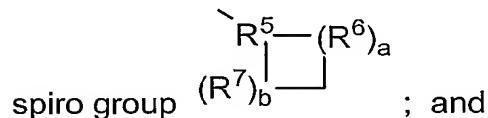
25 or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (IV) above:

A is selected from the group consisting of R^2 -substituted heterocycloalkyl, R^2 -substituted heteroaryl, R^2 -substituted benzofused heterocycloalkyl, and R^2 -substituted benzofused heteroaryl;

5 Ar^1 is aryl or R^3 -substituted aryl;

Ar^2 is aryl or R^4 -substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the



R^1 is selected from the group consisting of:

$-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can

10 also be zero or 1;

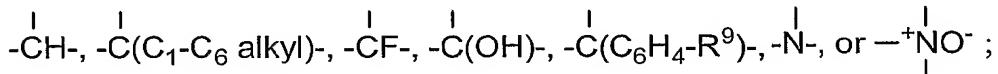
$-(CH_2)_e-G-(CH_2)_r-$, wherein G is $-O-$, $-C(O)-$, phenylene, $-NR^8-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

$-(C_2-C_6 \text{ alkenylene})-$; and

$-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1-5 and g is 0-5,

15 provided that the sum of f and g is 1-6;

R^5 is selected from:

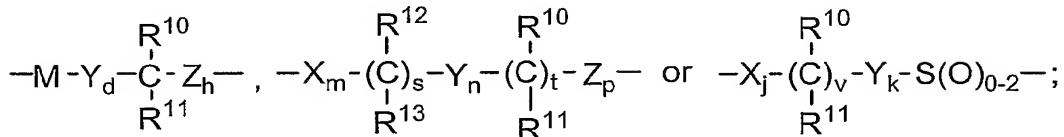


R^6 and R^7 are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6 \text{ alkyl})-$, $-C(\text{di-}(C_1-C_6) \text{ alkyl})$, $-CH=CH-$ and

20 $-C(C_1-C_6 \text{ alkyl})=CH-$; or R^5 together with an adjacent R^6 , or R^5 together with an adjacent R^7 , form a $-CH=CH-$ or a $-CH=C(C_1-C_6 \text{ alkyl})-$ group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^6 is $-CH=CH-$ or $-C(C_1-C_6 \text{ alkyl})=CH-$, a is 1; provided that when R^7 is $-CH=CH-$ or $-C(C_1-C_6 \text{ alkyl})=CH-$, b is 1; provided that when a is 2 or 3, the R^6 's can be the same or different; and provided that when b is 2 or 3, the R^7 's can be the same or different;

and when Q is a bond, R¹ also can be selected from:



where M is -O-, -S-, -S(O)- or -S(O)₂;

X, Y and Z are independently selected from the group consisting of

5 -CH₂-, -CH(C₁-C₆ alkyl)- and -C(di-(C₁-C₆) alkyl);

R¹⁰ and R¹² are independently selected from the group consisting of -OR¹⁴, -O(CO)R¹⁴, -O(CO)OR¹⁶ and -O(CO)NR¹⁴R¹⁵;

R¹¹ and R¹³ are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl and aryl; or R¹⁰ and R¹¹ together are =O, or R¹² and R¹³ together are =O;

10 d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

R² is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl,

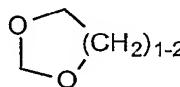
20 (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, R¹⁷-substituted aryl, R¹⁷-substituted benzyl,

R¹⁷-substituted benzyloxy, R¹⁷-substituted aryloxy, halogeno, -NR¹⁴R¹⁵,

NR¹⁴R¹⁵(C₁-C₆ alkylene)-, NR¹⁴R¹⁵C(O)(C₁-C₆ alkylene)-, -NHC(O)R¹⁶,

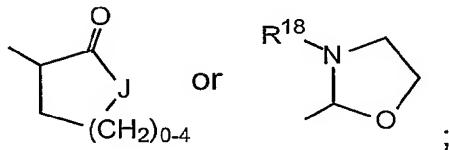
OH, C₁-C₆ alkoxy, -OC(O)R¹⁶, -COR¹⁴, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-

C₆)alkyl, NO₂, -S(O)₀₋₂R¹⁶, -SO₂NR¹⁴R¹⁵ and -(C₁-C₆ alkylene)COOR¹⁴; when R² is a

25 substituent on a heterocycloalkyl ring, R² is as defined, or is =O or ; and, where R² is a substituent on a substitutable ring nitrogen, it is hydrogen,

- 50 -

(C₁-C₆)alkyl, aryl, (C₁-C₆)alkoxy, aryloxy, (C₁-C₆)alkylcarbonyl, arylcarbonyl, hydroxy, -(CH₂)₁₋₆CONR¹⁸R¹⁸,



wherein J is -O-, -NH-, -NR¹⁸- or -CH₂-;

5 R³ and R⁴ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₁-C₆)alkyl, -OR¹⁴, -O(CO)R¹⁴, -O(CO)OR¹⁶, -O(CH₂)₁₋₅OR¹⁴, -O(CO)NR¹⁴R¹⁵, -NR¹⁴R¹⁵, -NR¹⁴(CO)R¹⁵, -NR¹⁴(CO)OR¹⁶, -NR¹⁴(CO)NR¹⁵R¹⁹, -NR¹⁴SO₂R¹⁶, -COOR¹⁴, -CONR¹⁴R¹⁵, -COR¹⁴, -SO₂NR¹⁴R¹⁵, S(O)₀₋₂R¹⁶, -O(CH₂)₁₋₁₀-COOR¹⁴, 10 -O(CH₂)₁₋₁₀CONR¹⁴R¹⁵, -(C₁-C₆)alkylene)-COOR¹⁴, -CH=CH-COOR¹⁴, -CF₃, -CN, -NO₂ and halogen;

R⁸ is hydrogen, (C₁-C₆)alkyl, aryl (C₁-C₆)alkyl, -C(O)R¹⁴ or -COOR¹⁴;

15 R⁹ and R¹⁷ are independently 1-3 groups independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -COOH, NO₂, -NR¹⁴R¹⁵, OH and halogeno;

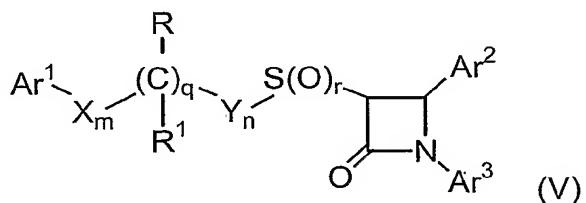
R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, aryl and aryl-substituted (C₁-C₆)alkyl;

R¹⁶ is (C₁-C₆)alkyl, aryl or R¹⁷-substituted aryl;

R¹⁸ is hydrogen or (C₁-C₆)alkyl; and

20 R¹⁹ is hydrogen, hydroxy or (C₁-C₆)alkoxy;

(d) Formula (V):



or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (V) above:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X and Y are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(dilower alkyl)-;

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁹ or -O(CO)NR⁶R⁷; R¹ is hydrogen, lower alkyl or aryl; or R and R¹ together are =O;

q is 0 or 1;

r is 0, 1 or 2;

m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀₋₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁵ is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀₋₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -CF₃, -CN, -NO₂, halogen, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

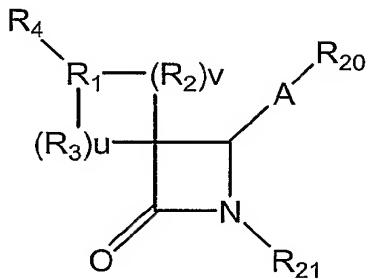
R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and

R¹⁰ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷,

$-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^9$, $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$,
 $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $-\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^6$,
 $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen;

5 (e) Formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein in Formula (VI):

10 R₁ is

$-\text{CH}-$, $-\text{C}(\text{lower alkyl})-$, $-\text{CF}-$, $-\text{C}(\text{OH})-$, $-\text{C}(\text{C}_6\text{H}_5)-$, $-\text{C}(\text{C}_6\text{H}_4\text{-R}_{15})-$,
 $-\text{N}-$ or $-\text{N}^+\text{O}^-$;

R₂ and R₃ are independently selected from the group consisting of:

$-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$, $-\text{C}(\text{di-lower alkyl})-$, $-\text{CH}=\text{CH}-$ and $-\text{C}(\text{lower alkyl})=\text{CH}-$; or

15 R₁ together with an adjacent R₂, or R₁ together with an adjacent R₃, form a
 $-\text{CH}=\text{CH}-$ or a $-\text{CH}=\text{C}(\text{lower alkyl})-$ group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R₂ is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{lower alkyl})=\text{CH}-$, v is 1; provided that when R₃ is

$-\text{CH}=\text{CH}-$ or $-\text{C}(\text{lower alkyl})=\text{CH}-$, u is 1; provided that when v is 2 or 3, the R₂'s can

20 be the same or different; and provided that when u is 2 or 3, the R₃'s can be the same or different;

R₄ is selected from B-(CH₂)_mC(O)-, wherein m is 0, 1, 2, 3, 4 or 5;
 $\text{B}-(\text{CH}_2)_q-$, wherein q is 0, 1, 2, 3, 4, 5 or 6;

B-(CH₂)_e-Z-(CH₂)_r-, wherein Z is -O-, -C(O)-, phenylene, -N(R₈)- or -S(O)O-2-, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6;

B-(C₂-C₆ alkenylene)-;

5 B-(C₄-C₆ alkadienylene)-;

B-(CH₂)_t-Z-(C₂-C₆ alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

10 B-(CH₂)_f-V-(CH₂)_g-, wherein V is C₃-C₆ cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

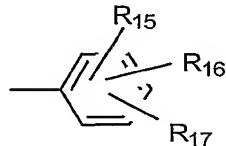
B-(CH₂)_t-V-(C₂-C₆ alkenylene)- or

B-(C₂-C₆ alkenylene)-V-(CH₂)_t-, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

15 B-(CH₂)_a-Z-(CH₂)_b-V-(CH₂)_d-, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6; or T-(CH₂)_s-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

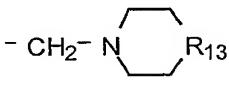
R₁ and R₄ together form the group B-CH=C- ;

20 B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



25 W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, -CF₃, -OCF₃, benzyl, R₇-benzyl, benzyloxy,

R₇-benzyloxy, phenoxy, R₇-phenoxy, dioxolanyl, NO₂, -N(R₈)(R₉), N(R₈)(R₉)-lower alkylene-, N(R₈)(R₉)-lower alkyleneoxy-, OH, halogeno, -CN, -N₃, -NHC(O)OR₁₀, -NHC(O)R₁₀, R₁₁O₂SNH-, (R₁₁O₂S)₂N-, -S(O)₂NH₂, -S(O)O-2R₈, tert-
5 butyldimethyl-silyloxymethyl, -C(O)R₁₂, -COOR₁₉, -CON(R₈)(R₉), -CH=CHC(O)R₁₂, -lower alkylene-C(O)R₁₂, R₁₀C(O)(lower alkyleneoxy)-, N(R₈)(R₉)C(O)(lower

10 alkyleneoxy)- and  for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OR₁₀, -C(O)R₁₀, OH, N(R₈)(R₉)-lower alkylene-, N(R₈)(R₉)-lower alkyleneoxy-, -S(O)₂NH₂ and 2-(trimethylsilyl)-ethoxymethyl;

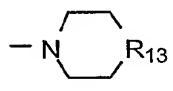
15 R₇ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO₂, -N(R₈)(R₉), OH, and halogeno;

R₈ and R₉ are independently selected from H or lower alkyl;

20 R₁₀ is selected from lower alkyl, phenyl, R₇-phenyl, benzyl or R₇-benzyl;

R₁₁ is selected from OH, lower alkyl, phenyl, benzyl, R₇-phenyl or R₇-benzyl;

R₁₂ is selected from H, OH, alkoxy, phenoxy, benzyloxy,

 -N(R₈)(R₉), lower alkyl, phenyl or R₇-phenyl;

R₁₃ is selected from -O-, -CH₂-, -NH-, -N(lower alkyl)- or -NC(O)R₁₉;

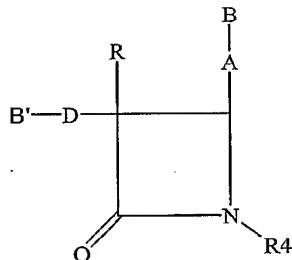
25 R₁₅, R₁₆ and R₁₇ are independently selected from the group consisting of H and the groups defined for W; or R₁₅ is hydrogen and R₁₆ and R₁₇, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R₁₉ is H, lower alkyl, phenyl or phenyl lower alkyl; and

R₂₀ and R₂₁ are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above;

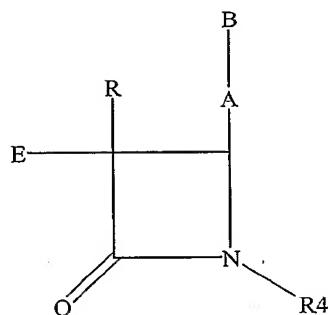
- 55 -

(f) Formula (VIIA) or (VIIIB):



(VIIA)

or

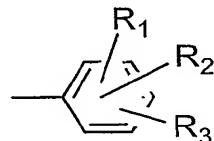


(VIIIB)

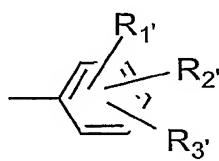
or a pharmaceutically acceptable salt or solvate thereof, wherein in Formulae (VIIA) or (VIIIB):

A is $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$ or $-(\text{CH}_2)_p-$ wherein p is 0, 1 or 2;

10 B is



B' is



D is $-(\text{CH}_2)_m\text{C}(\text{O})-$ or $-(\text{CH}_2)_q-$ wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

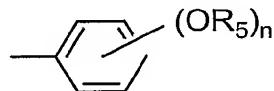
15 E is C₁₀ to C₂₀ alkyl or $-\text{C}(\text{O})-(\text{C}_9 \text{ to } \text{C}_{19})\text{alkyl}$, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

- 56 -

R is hydrogen, C1-C15 alkyl, straight or branched, saturated or containing one or more double bonds, or B-(CH₂)_r-, wherein r is 0, 1, 2, or 3;

5 R₁, R₂, R₃, R_{1'}, R_{2'}, and R_{3'} are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO₂, NH₂, OH, halogeno, lower alkylamino, dilower alkylamino, -NHC(O)OR₅, R₆O₂SNH- and -S(O)₂NH₂;

R₄ is

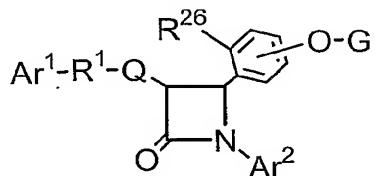


wherein n is 0, 1, 2 or 3;

R₅ is lower alkyl; and

10 R₆ is OH, lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO₂, NH₂, OH, halogeno, lower alkylamino and dilower alkylamino;

15 (g) Formula (VIII):

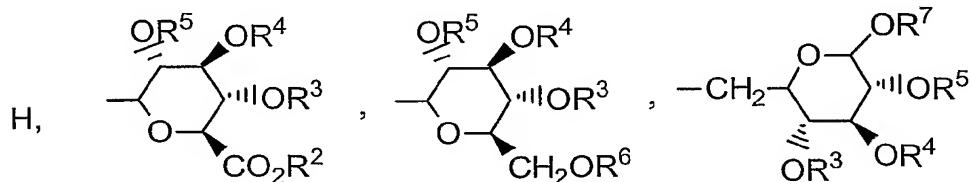


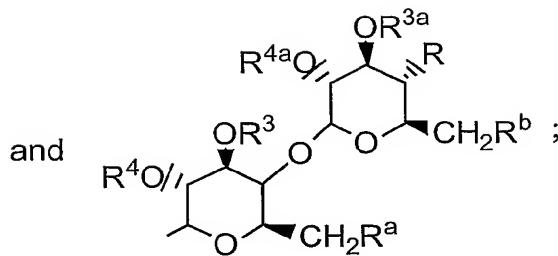
(VIII)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (VIII) above,

20 R²⁶ is H or OG¹;

G and G¹ are independently selected from the group consisting of





provided that when R²⁶ is H or

OH, G is not H;

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, -NH₂, azido, (C₁-C₆)alkoxy(C₁-C₆)-alkoxy or -W-R³⁰;

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R³¹)-, -NH-C(O)-N(R³¹)- and -O-C(S)-N(R³¹)-;

R² and R⁶ are independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl and aryl(C₁-C₆)alkyl;

R³, R⁴, R⁵, R⁷, R^{3a} and R^{4a} are independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, -C(O)(C₁-C₆)alkyl and -C(O)aryl;

R³⁰ is selected from the group consisting of R³²-substituted T, R³²-substituted-T-(C₁-C₆)alkyl, R³²-substituted-(C₂-C₄)alkenyl, R³²-substituted-(C₁-C₆)alkyl, R³²-substituted-(C₃-C₇)cycloalkyl and R³²-substituted-(C₃-C₇)cycloalkyl(C₁-C₆)alkyl;

R³¹ is selected from the group consisting of H and (C₁-C₄)alkyl;

T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

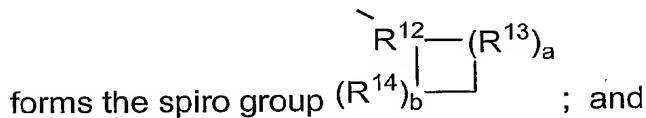
R³² is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C₁-C₄)alkyl, -OH, phenoxy, -CF₃, -NO₂, (C₁-C₄)alkoxy, methylenedioxy, oxo, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, -N(CH₃)₂, -C(O)-NH(C₁-C₄)alkyl, -C(O)-N((C₁-C₄)alkyl)₂, -C(O)-(C₁-C₄)alkyl, -C(O)-(C₁-C₄)alkoxy and pyrrolidinylcarbonyl; or R³² is a covalent bond and R³¹, the nitrogen to which it is

attached and R³² form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C₁-C₄)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar¹ is aryl or R¹⁰-substituted aryl;

5 Ar² is aryl or R¹¹-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone,



R¹ is selected from the group consisting of

-(CH₂)_q-, wherein q is 2-6, provided that when Q forms a spiro ring, q

10 can also be zero or 1;

-(CH₂)_e-E-(CH₂)_r-, wherein E is -O-, -C(O)-, phenylene, -NR²²- or

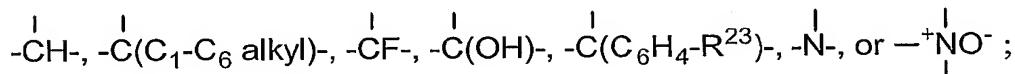
-S(O)O-2-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

-(C₂-C₆)alkenylene-; and

-(CH₂)_f-V-(CH₂)_g-, wherein V is C₃-C₆ cycloalkylene, f is 1-5 and g is 0-

15 5, provided that the sum of f and g is 1-6;

R¹² is



R¹³ and R¹⁴ are independently selected from the group consisting of -CH₂-,

-CH(C₁-C₆ alkyl)-, -C(di-(C₁-C₆) alkyl), -CH=CH- and

20 -C(C₁-C₆ alkyl)=CH-; or R¹² together with an adjacent R¹³, or R¹² together with an adjacent R¹⁴, form a -CH=CH- or a -CH=C(C₁-C₆ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero;

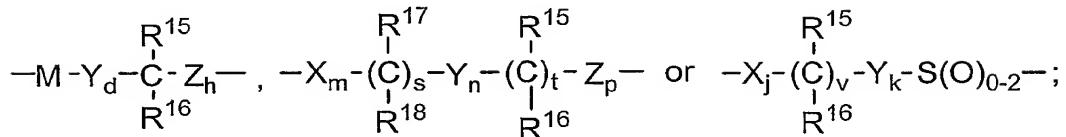
provided that when R¹³ is -CH=CH- or -C(C₁-C₆ alkyl)=CH-, a is 1;

provided that when R¹⁴ is -CH=CH- or -C(C₁-C₆ alkyl)=CH-, b is 1;

25 provided that when a is 2 or 3, the R¹³'s can be the same or different; and

provided that when b is 2 or 3, the R¹⁴'s can be the same or different;

and when Q is a bond, R¹ also can be:



M is -O-, -S-, -S(O)- or -S(O)2-;

X, Y and Z are independently selected from the group consisting of -CH₂-,

5 -CH(C₁-C₆)alkyl- and -C(di-(C₁-C₆)alkyl);

R¹⁰ and R¹¹ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of

(C₁-C₆)alkyl, -OR¹⁹, -O(CO)R¹⁹, -O(CO)OR²¹, -O(CH₂)₁₋₅OR¹⁹,

-O(CO)NR¹⁹R²⁰, -NR¹⁹R²⁰, -NR¹⁹(CO)R²⁰, -NR¹⁹(CO)OR²¹,

10 -NR¹⁹(CO)NR²⁰R²⁵, -NR¹⁹SO₂R²¹, -COOR¹⁹, -CONR¹⁹R²⁰, -COR¹⁹,

-SO₂NR¹⁹R²⁰, S(O)₀₋₂R²¹, -O(CH₂)₁₋₁₀-COOR¹⁹, -O(CH₂)₁₋₁₀CONR¹⁹R²⁰,

-(C₁-C₆)alkylene)-COOR¹⁹, -CH=CH-COOR¹⁹, -CF₃, -CN, -NO₂ and halogen;

R¹⁵ and R¹⁷ are independently selected from the group consisting of -OR¹⁹, -O(CO)R¹⁹, -O(CO)OR²¹ and -O(CO)NR¹⁹R²⁰;

15 R¹⁶ and R¹⁸ are independently selected from the group consisting of H,

(C₁-C₆)alkyl and aryl; or R¹⁵ and R¹⁶ together are =O, or R¹⁷ and R¹⁸ together are =O;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

20 s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4;

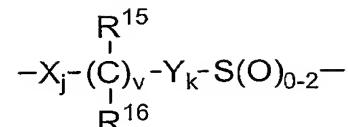
provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

25 j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

- 60 -



and when Q is a bond and R^1 is R^{16} , Ar^1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R^{19} and R^{20} are independently selected from the group consisting of H,

5 (C₁-C₆)alkyl, aryl and aryl-substituted (C₁-C₆)alkyl;

R^{21} is (C₁-C₆)alkyl, aryl or R^{24} -substituted aryl;

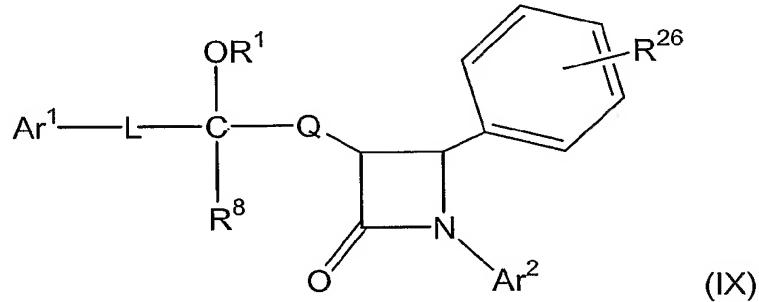
R^{22} is H, (C₁-C₆)alkyl, aryl (C₁-C₆)alkyl, -C(O)R¹⁹ or -COOR¹⁹;

R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -COOH, NO₂,

10 -NR¹⁹R²⁰, -OH and halogeno; and

R^{25} is H, -OH or (C₁-C₆)alkoxy; and

(h) Formula (IX):



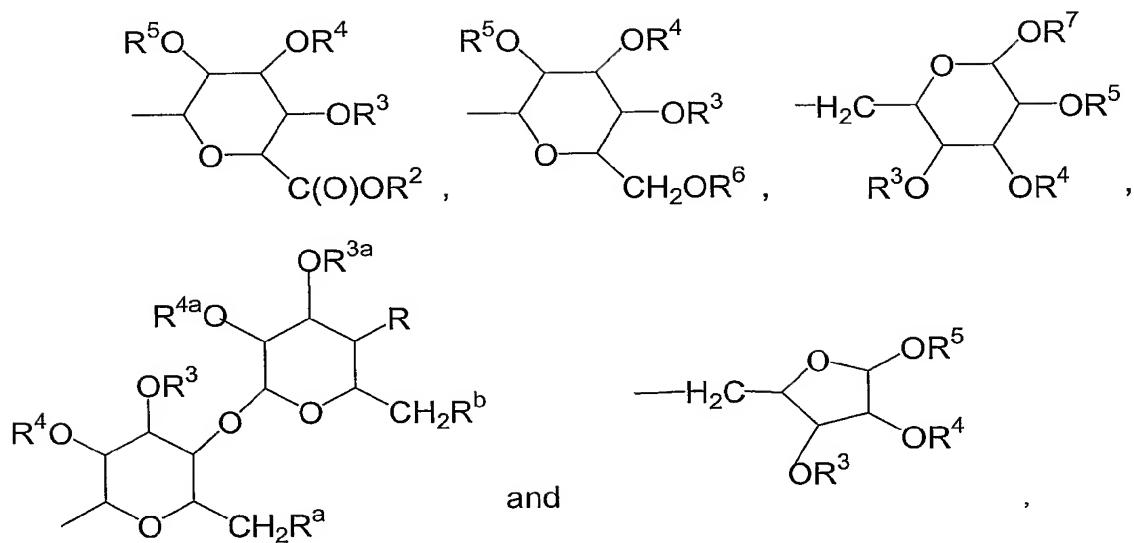
15

or a pharmaceutically acceptable salt or solvate thereof, wherein in Formula (IX):

R^1 is selected from the group consisting of H, G, G¹, G², -SO₃H and -PO₃H;

20 G is selected from the group consisting of: H,

- 61 -



wherein R, R^a and R^b are each independently selected from the group consisting of H, -OH, halo, -NH₂, azido, (C₁-C₆)alkoxy(C₁-C₆)alkoxy or -W-R³⁰;

5 W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R³¹)-, -NH-C(O)-N(R³¹)- and -O-C(S)-N(R³¹)-;

10 R² and R⁶ are each independently selected from the group consisting of H, (C₁-C₆)alkyl, acetyl, aryl and aryl(C₁-C₆)alkyl;

15 R³, R⁴, R⁵, R⁷, R^{3a} and R^{4a} are each independently selected from the group consisting of H, (C₁-C₆)alkyl, acetyl, aryl(C₁-C₆)alkyl, -C(O)(C₁-C₆)alkyl and -C(O)aryl;

20 R³⁰ is independently selected from the group consisting of R³²-substituted T, R³²-substituted-T-(C₁-C₆)alkyl, R³²-substituted-(C₂-C₄)alkenyl, R³²-substituted-(C₁-C₆)alkyl, R³²-substituted-(C₃-C₇)cycloalkyl and R³²-substituted-(C₃-C₇)cycloalkyl(C₁-C₆)alkyl;

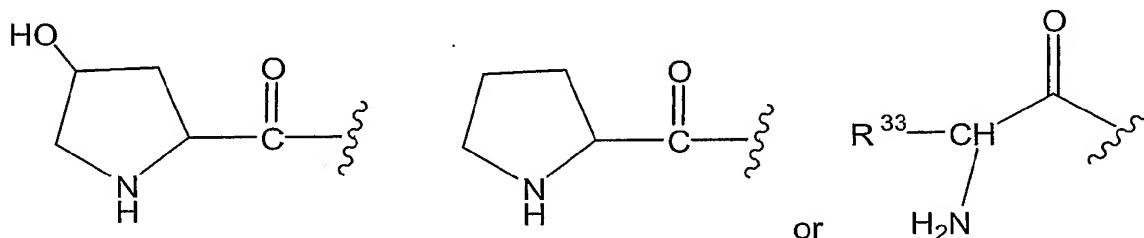
- 62 -

R^{31} is independently selected from the group consisting of H and (C₁-C₄)alkyl;

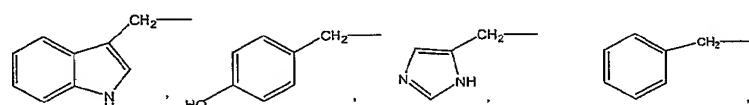
T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, 5 pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents which are each independently selected from the group consisting of H, halo, (C₁-C₄)alkyl, -OH, phenoxy, -CF₃, -NO₂, (C₁-C₄)alkoxy, methylenedioxy, oxo, (C₁-C₄)alkylsulfanyl, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, -N(CH₃)₂, -C(O)-NH(C₁-C₄)alkyl, -C(O)-N((C₁-C₄)alkyl)₂, -C(O)-(C₁-C₄)alkyl, -C(O)-(C₁-C₄)alkoxy and pyrrolidinylcarbonyl; or R^{32} 10 is a covalent bond and R^{31} , the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C₁-C₄)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or 15 morpholinyl group;

G^1 is represented by the structure:



wherein R^{33} is independently selected from the group consisting of unsubstituted alkyl, R^{34} -substituted alkyl, (R^{35})(R^{36})alkyl-, 20

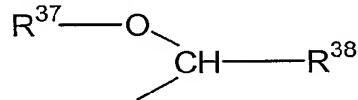


R^{34} is one to three substituents, each R^{34} being independently selected from the group consisting of HOOC-, HO-, HS-, (CH₃)S-, H₂N-, (NH₂)(NH)C(NH)-, (NH₂)C(O)- and HOOCCH(NH₃⁺)CH₂SS-;

R^{35} is independently selected from the group consisting of H and NH_2 ;

R^{36} is independently selected from the group consisting of H, unsubstituted alkyl, R^{34} -substituted alkyl, unsubstituted cycloalkyl and R^{34} -substituted cycloalkyl;

5 G^2 is represented by the structure:



wherein R^{37} and R^{38} are each independently selected from the group consisting of (C_1-C_6)alkyl and aryl;

10

R^{26} is one to five substituents, each R^{26} being independently selected from the group consisting of:

- a) H;
- b) -OH;
- c) - OCH_3 ;
- d) fluorine;
- e) chlorine;
- f) - $O-G$;
- g) - $O-G^1$;
- h) - $O-G^2$;
- i) - SO_3H ; and
- j) - PO_3H ;

15

provided that when R^1 is H, R^{26} is not H, -OH, - OCH_3 or - $O-G$;

20

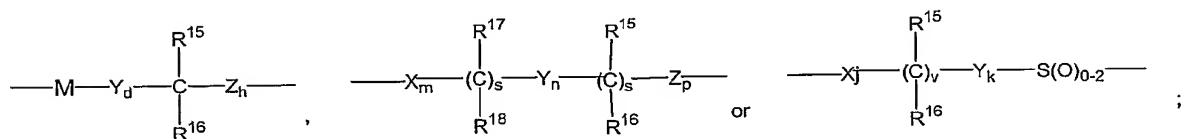
Ar^1 is aryl, R^{10} -substituted aryl, heteroaryl or R^{10} -substituted heteroaryl;

Ar^2 is aryl, R^{11} -substituted aryl, heteroaryl or R^{11} -substituted heteroaryl;

25

L is selected from the group consisting of:

- a) a covalent bond;
- b) $-(CH_2)_q-$, wherein q is 1-6;
- c) $-(CH_2)_e-E-(CH_2)_r-$, wherein E is $-O-$, $-C(O)-$, phenylene, $-NR^{22}-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;
- 5 d) $-(C_2-C_6)$ alkenylene-;
- e) $-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; and
- f)



10

wherein M is $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;

X, Y and Z are each independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6)$ alkyl- and $-C(di-(C_1-C_6)alkyl)-$;

15

R^8 is selected from the group consisting of H and alkyl;

20

R^{10} and R^{11} are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of (C_1-C_6) alkyl, $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$, $-O(CH_2)_{1-5}OR^{19}$, $-O(CO)NR^{19}R^{20}$, $-NR^{19}R^{20}$, $-NR^{19}(CO)R^{20}$, $-NR^{19}(CO)OR^{21}$, $-NR^{19}(CO)NR^{20}R^{25}$, $-NR^{19}SO_2R^{21}$, $-COOR^{19}$, $-CONR^{19}R^{20}$, $-COR^{19}$, $-SO_2NR^{19}R^{20}$, $S(O)_{0-2}R^{21}$, $-O(CH_2)_{1-10}COOR^{19}$, $-O(CH_2)_{1-10}CONR^{19}R^{20}$, $-(C_1-C_6)$ alkylene)- $COOR^{19}$, $-CH=CH-COOR^{19}$, $-CF_3$, $-CN$, $-NO_2$ and halo;

25

R^{15} and R^{17} are each independently selected from the group consisting of $-OR^{19}$, $-OC(O)R^{19}$, $-OC(O)OR^{21}$, $-OC(O)NR^{19}R^{20}$;

- 65 -

R^{16} and R^{18} are each independently selected from the group consisting of H, (C₁-C₆)alkyl and aryl;

or R^{15} and R^{16} together are =O, or R^{17} and R^{18} together are =O;

5

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

s is 0 or 1;

t is 0 or 1;

10 m , n and p are each independently selected from 0-4;

provided that at least one of s and t is 1, and the sum of m , n , p , s and t is 1-6;

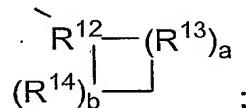
provided that when p is 0 and t is 1, the sum of m , n and p is 1-5; and provided that

when p is 0 and s is 1, the sum of m , t and n is 1-5;

v is 0 or 1;

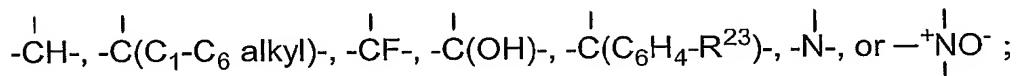
15 j and k are each independently 1-5, provided that the sum of j , k and v is 1-5;

Q is a bond, -(CH₂)_q-, wherein q is 1-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group



20

wherein R^{12} is

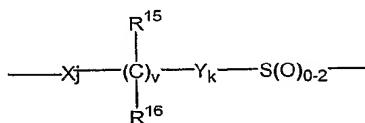


25 R^{13} and R^{14} are each independently selected from the group consisting of -CH₂-, -CH(C₁-C₆ alkyl)-, -C(di-(C₁-C₆) alkyl), -CH=CH- and -C(C₁-C₆ alkyl)=CH-; or R^{12} together with an adjacent R^{13} , or R^{12} together with an adjacent R^{14} , form a -CH=CH- or a -CH=C(C₁-C₆ alkyl)- group;

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a and b are each independently 0, 1, 2 or 3, provided both are not zero; provided that when R¹³ is -CH=CH- or -C(C₁-C₆ alkyl)=CH-, a is 1; provided that when R¹⁴ is -CH=CH- or -C(C₁-C₆ alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R¹³'s can be the same or different; and provided that when b is 2 or 3, the R¹⁴'s can be the same or different;

5 and when Q is a bond and L is



10

then Ar¹ can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

15 R¹⁹ and R²⁰ are each independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl and aryl-substituted (C₁-C₆)alkyl;

R²¹ is (C₁-C₆)alkyl, aryl or R²⁴-substituted aryl;

R²² is H, (C₁-C₆)alkyl, aryl (C₁-C₆)alkyl, -C(O)R¹⁹ or -COOR¹⁹;

20

R²³ and R²⁴ are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -COOH, NO₂, -NR¹⁹R²⁰, -OH and halo; and

25 R²⁵ is H, -OH or (C₁-C₆)alkoxy.

3. The method according to claim 1, wherein the at least one sterol absorption inhibitor is administered to a subject in an amount ranging from about 0.1 to about 1000 milligrams of sterol absorption inhibitor per day.

4. The method according to claim 1, further comprising the step of administering at least one antidyemyelination agent to the subject.

5 5. The method according to claim 4, wherein the antidyemyelination agent is selected from the group consisting of beta interferon, glatiramer acetate and corticosteroids.

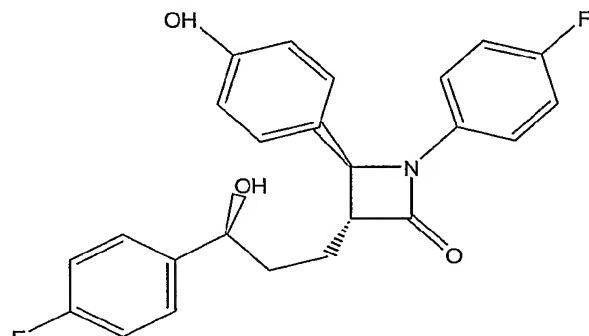
10 6. The method according to claim 1, further comprising the step of administering at least one HMG CoA reductase inhibitor to the subject.

7. The method according to claim 6, wherein the at least one HMG CoA reductase inhibitor is atorvastatin.

15 8. The method according to claim 6, wherein the at least one HMG CoA reductase inhibitor is simvastatin.

9. The method according to claim 1, wherein the subject has multiple sclerosis.

20 10. A method of treating or preventing demyelination in a subject is provided, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor represented by Formula (II) below:



or a pharmaceutically acceptable salt or solvate thereof.

11. A method of treating or preventing multiple sclerosis in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof.

12. A composition comprising: (a) at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof and (b) at least one 10 antidemyelination agent.

13. A therapeutic combination comprising: (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof; and (b) a second amount of at least one antidemyelination agent, wherein the first amount 15 and the second amount together comprise a therapeutically effective amount for the treatment or prevention of demyelination in a subject.

14. Use of at least one compound of at least one of claims 1 or 2 for manufacture of a medicament for treatment of demyelination in a subject.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/35027

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/397 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03/082192 A (SMITHKLINE BEECHAM CORP ;MA CHUM (US); BHAT AJITA (US); FRAZEE JAM) 9 October 2003 (2003-10-09) page 23, line 10-30; claim 37 -----	1,11
X	WO 02/070523 A (DIDIUK MARY THERESA ;GARIGIPATI RAVI SHANKER (US); LAU WAN FANG (U) 12 September 2002 (2002-09-12) page 13, line 29 -page 14, line 18; claims 8,14 -----	1,12-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 April 2004

Date of mailing of the international search report

21/04/2004

Name and mailing address of the ISA

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NL-2280 HV Rijswijk
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Authorized officer

Friederich, M

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT – Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Present claims 1-8, 10 and 12-14 relate to a method/composition defined by reference to desirable characteristics or properties, namely "sterol absorption inhibitor" and "demyelination".

The claims cover all methods/compositions having this characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods/compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method/composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds I-XII mentioned in claim 2 and the diseases mentioned in the description at page 1, lines 19-32.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/35027

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. Claims Nos.: —
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: —
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/35027

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03082192	A	09-10-2003	WO	03082192 A2
				09-10-2003
WO 02070523	A	12-09-2002	CA	2440803 A1
			EP	1368354 A1
			WO	02070523 A1
			US	2003008893 A1
				12-09-2002
				10-12-2003
				12-09-2002
				09-01-2003

INTERNATIONAL SEARCH REPORT

PCT REQUEST

Original (for SUBMISSION) - printed on 04.11.2003 02:57:22 PM

4/0
CV01679

VIII-2-1	<p>Declaration: Entitlement to apply for and be granted a patent</p> <p>Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:</p> <p>Name:</p>	<p>in relation to this international application</p> <p>SCHERING CORPORATION is entitled to apply for and be granted a patent by virtue of the following:</p>
VIII-2-1 (iv)		an assignment from FINE, Jay, S. to SCHERING CORPORATION, dated 28 October 2003 (28.10.2003)
VIII-2-1 (iv)		an assignment from PARKER, Eric, McFee to SCHERING CORPORATION, dated 28 October 2003 (28.10.2003)
VIII-2-1 (ix)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

INTERNATIONAL SEARCH REPORT

PCT REQUEST

Original (for SUBMISSION) - printed on 04.11.2003 02:57:22 PM

CV01679

VIII-2-2	<p>Declaration: Entitlement to apply for and be granted a patent</p> <p>Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:</p> <p>Name:</p>	<p>in relation to this international application</p> <p>SCHERING CORPORATION is entitled to apply for and be granted a patent by virtue of the following:</p>
VIII-2-2 (iv)		<p>an assignment from ERBEY, John, R., II to SCHERING CORPORATION, dated 18 September 2003 (18.09.2003)</p>
VIII-2-2 (iv)		<p>an assignment from FINE, Jay, S. to SCHERING CORPORATION, dated 28 October 2003 (28.10.2003)</p>
VIII-2-2 (iv)		<p>an assignment from VELTRI, Enrico, P. to SCHERING CORPORATION, dated 28 October 2003 (28.10.2003)</p>
VIII-2-2 (ix)	<p>This declaration is made for the purposes of:</p>	<p>all designations except the designation of the United States of America</p>

INTERNATIONAL SEARCH REPORT

PCT REQUEST

Original (for SUBMISSION) - printed on 04.11.2003 02:57:22 PM

CV01679

VIII-3-1	<p>Declaration: Entitlement to claim priority</p> <p>Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)).</p> <p>Name:</p>	<p>in relation to this international application</p> <p>SCHERING CORPORATION is entitled to claim priority of earlier application No. 60/424,165 by virtue of the following:</p>
VIII-3-1 (iv)		<p>an assignment from FINE, Jay, S. to SCHERING CORPORATION, dated 18 December 2002 (18.12.2002)</p>
VIII-3-1 (iv)		<p>an assignment from PARKER, Eric, McFee to SCHERING CORPORATION, dated 18 December 2002 (18.12.2002)</p>
VIII-3-1 (ix)	This declaration is made for the purposes of:	all designations

INTERNATIONAL SEARCH REPORT

1/0

PCT REQUEST

CV01679

Original (for **SUBMISSION**) - printed on 04.11.2003 02:57:22 PM

VIII-3-2	<p>Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(III) and 51bis.1(a)(iii)): Name:</p>	<p>in relation to this international application</p> <p>SCHERING CORPORATION is entitled to claim priority of earlier application No. 60/493,318 by virtue of the following:</p>
VIII-3-2 (iv)		an assignment from ERBEY, John, R., II to SCHERING CORPORATION, dated 07 August 2003 (07.08.2003)
VIII-3-2 (iv)		an assignment from FINE, Jay, S. to SCHERING CORPORATION, dated 07 August 2003 (07.08.2003)
VIII-3-2 (iv)		an assignment from VELTRI, Enrico, P. to SCHERING CORPORATION, dated 07 August 2003 (07.08.2003)
VIII-3-2 (ix)	This declaration is made for the purposes of:	all designations